Patients centred pharmacovigilance

Thesis

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Abstract

In recent years, periodically high peaks of attention and publications have documented severe adverse reactions to new molecules, which have raised many questions about the efficacy-efficiency of traditional methodological tools of pharmacovigilance, as well as about the role of regulatory systems. Drugs cannot be considered as an independent variable: the evaluation of all of their effects must take into account the real context in which they are used, and in which they are expected have a role, not only in terms of efficacy, but also of tolerability and safety. Specific emphasis is given to recent and promising developments, which are focused on the participation of patient populations as *key actors* in producing knowledge that can also technically integrate what has been produced so far, and can allow the evolution of surveillance from a role of control to one of the promotion of rights. The replacement of pharmacovigilance in an epidemiological context is the main aim of this project. This is applied across the development of various projects realised in different scenarios (e.g. hospital, community) using different methodologies (e.g. administrative database linkage, prospective studies, qualitative projects), and through the direct involvement of all of the actors involved in the process of care (e.g. clinicians, general practitioners, patients). In particular, despite the many recommendations, patient participation can be considered as an exception in the health care setting: for this reason the project was developed with the intention to give *voice* to patients. Promotion of the use of a more narrative style between health professionals and citizen-patients in pharmacovigilance should be considered the most important outcome of a renewed pharmacovigilance.

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CHAPTER 1

Introduction: a historical and methodological re-assessment of pharmacovigilance.

1.1 General frame of reference.

Over the past fifty years, the scientific and regulatory literature directly or indirectly referring to the area of drug surveillance has been an important protagonist in pharmacology, public health, epidemiology and clinical debate. Greater attention and more publications have coincided with events related to severe adverse reactions (SARs) of particular relevance and impact, such as in the list in Table 1.1, which is, however, far from being exhaustive.

Whatever the terminology with which SARs are defined and documented in clinical trials, spontaneous reports, or any kind of register, their operative definition is clear: they are cases, clusters, groups or populations in which the expected outcome of a certain pharmacological intervention that is registered and sold on the basis of a favourable or acceptable risk-benefit balance turns into a documented observation of a reversal of this balance. This can arrive at the point where a more or less drastic modification of the drug status with respect to its prescription and/or marketing is required.

Table 1.1 – *Memorandum of pharmacovigilance history through sentinel events.*

Drug	Adverse reaction	Year of withdrawal
Thalidomide	Teratogenicity	1961
Practolol	Oculo-mucocutaneous syndrome	1976
Phenacetin	Nephropathy	1980
Benoxaprofen	Jaundice	1982
Tolcapone	Hepatoxicity	1998
Trovafloxacin	Hepatoxicity	1999
Cisapride	Cardiac arrhythmias; QT prolongation	2000
Cerivastatin	Rhabdomyolysis	2001
Rofecoxib, Valdecoxib	Myocardial infarction	2004-2005
Rosiglitazone	Myocardial infarction	2010
Sibutramine	Cardiovascular disease	2010

Note: These examples include only the few drugs where the withdrawal has provoked heated debate in the media (and therefore within the public domain) and has not simply been restricted to the medical profession.

Keeping in mind some of the most recent interpretations of the development, roles, results and limits of pharmacovigilance (PV) (1-4), the aim of this project is to explore if and to what extent the overall scenario requires some degree of cultural and methodological discontinuity in the way of thinking about, and therefore applying, PV: not so much with the intent of denying or arguing its specific importance and substantial objectives, as of discussing and outlining developments that can allow its deeper understanding and integration into the current reality of medicine and society.

The courses of action proposed here to verify this hypothesis are relatively simple:

a) a concise and 'specific' review of PV (a knowledge of which is assumed, in terms of the above mentioned literature);

b) the placement of PV within the methodological and institutional evolution that has characterised the evaluation process of drugs and their role in medicine;

c) a motivated reformulation of the roles and contents of PV in the perspective of an 'epidemiology of care', defined as the overall events (benefit + risk + appropriateness + acceptability + sustainability) that occur in the populations (and/or subgroups, individuals) when their needs require (and receive) intervention and services (pharmacological and non-pharmacological) available within the health system.

1.2 Essential elements in the history of pharmacovigilance.

The chronology of the development of PV is summarised in Table 1.2, although this does not claim to be exhaustive; it aims to provide a framework of reference to allow the methodological and institutional stages of PV to be better placed in their time context, as they are 'interpreted' in Figure 1.1.

Table 1.2 – *Some of the significant stages in the development of pharmacovigilance.*

Year	Description
1937	Food and Drug Administration (FDA) starts to register adverse drug reactions following a few sudden deaths due to poisoning by an elixir of sulphanilamide (with diethylene glycol as vehicle).

Year	Description
1961	The tragedy of thalidomide malformations represents a turning point in the perception of safety problems and of the risk of insufficiently controlled market approval (5).
1961-65	Following the thalidomide disaster, national centres monitoring adverse drug reactions are developed in Europe.
1963	Following the thalidomide disaster, the **Committee on the Safety of Medicines (CSM)** that is designed to monitor new drugs was set up in Great Britain; for 40 years the CSM has alerted the UK Licensing Authority on drug quality, efficacy and safety. In 2005, the CSM was replaced by the Commission on Human Medicine.
1963	The World Health Assembly adopted a resolution (WHA 16.36) reaffirming the need to promote more attention and surveillance of adverse drug reactions.
1968	The World Health Organisation (WHO) launches the *Pilot Research Project for International Drug Monitoring*, which was subsequently developed as the *WHO Programme for International Drug Monitoring,* currently coordinated by the *Uppsala Monitoring Centre* in Sweden.
1971	A WHO Consultation Meeting formalises the need for national centres for drug monitoring and for reference centres in charge of further studies on drug-related problems.
1980	The *Council for International Organisations of Medical Sciences* (CIOMS) launches the programme for drug development and use, which includes recommendations (to policy makers, the drug industry, governments, academics) to improve the exchange of safety information between the drug industry and the regulatory agencies.
2001	The EudraVigilance international network is set-up by the European Medicines Agency (EMA), which includes all adverse reaction reports to drugs authorised in the European Union, that must be forwarded by regulatory agencies and drug industries to the EU.
2005	Introduction of the Risk Management Plan by the EMA.

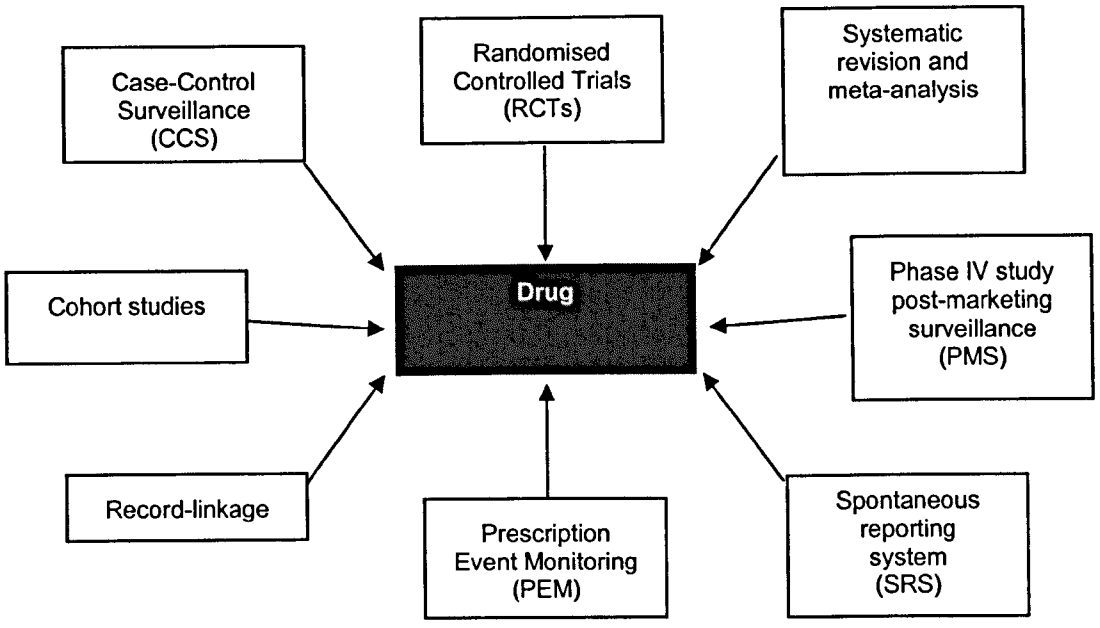

Figure 1.1: *Pharmacovigilance strategy and methodology.*

The following points relate to the general PV scenario:

1. An overall evaluation of the available literature on PV concerning both its methodology and regulatory aspects must point out its substantially repetitive and redundant contents, with many reiterated recommendations (both general and specific) on what could or should be done to avoid periodical clinical-epidemiological events that appear to document the failure of the current surveillance techniques, and are therefore discussed each time in terms of ineffectiveness or inefficiency of the prevention or of the timely identification of SARs.
2. The PV literature is particularly repetitive with respect to the recommended methodologies. The entire set of practicable designs was already complete at the end of the 1970's, or at most in the early 1980's. With the exception of the regular activities of the World Health

Organisation (WHO) system based on spontaneous reporting, it is clear that the substantial failure of PV strategies cannot be attributed to the lack of instruments, but points instead to the lack of coherent and effective policies.

Other strategies are more often represented by *ad-hoc* studies (which rarely show high methodological quality) than by a widespread and regularly functioning PV system (although there are obviously several exceptions to this general statement, at both the local and national levels) (6-10).

3. To provide a more concrete description of the distance between what could or should be changed, and what actually happens, it might be helpful to compare the PV area with the field of clinical experimentation. Between the 1970's and 1980's, the 'discovery' of the importance of the changing of the paradigm (not simply adjusting a study design or size) in terms of the representativeness of populations led to the era of population trials and large multicentre and increasingly international networks. This also outdated one of the first reasons for PV; i.e. that of compensating the small, non-representative trial populations, where sufficient highlighting of safety aspects was not allowed for.

   The establishment of systematic reviews in the most critical areas of therapy further emphasised the insufficient 'audacity' of PV in terms of technological innovation: in the classic benefit/ risk (B/R) ratio, the B variable dominates the picture. Interestingly, the R component has never become an object of regular interest even in the field of systematic reviews (nor is this due to methodological reasons).

4. The unsatisfactory efficiency of PV methodologies cannot reasonably be attributed to a lack of expertise or of willingness on the part of the professionals; rather, it indicates structural problems. A fundamental textbook started its publication under the responsibility

of Dukes (11), one of the main promoters of PV, who envisaged PV also in cultural and institutional terms. An important addition to this manual was the development of *ad-hoc* journals, and of publications that provided innovations to the language and methodology of PV, with a new focus also on the culture of accountability of their causes and/or the legal implications (12).

The "Seven Pillars of Foolishness" (13) represents the most lucid diagnosis of the structural difficulties of transforming PV into an activity that is capable of taking responsibility for the safety aspects of drugs, or, better still, for the B/R profile attributable to real populations. When drugs enter the market, evaluation in terms of outcome measures (both positive and unfavourable) drastically decreases, even though repeated recommendations are encouraged to guarantee and assess *ad-hoc* post-marketing studies. An indicator of the secondary importance attributed to the monitoring of R is the size of the economic resources allocated, which is orders of magnitude lower than that available for clinical trials (the studies 'prescribed' by the European Medicines Agency [EMA] to monitor the post-registration life of drugs for which insufficient documentation is available are a paradigm in this respect). This is all the more suspicious in light of the well known fact that pressures and conflicts of interest are increasingly present in the market context, which are even more widespread and effective than those that emerge in the controlled experimentation phases; one of the most recent cases is a model of this (14).

5. In the perspective of this thesis, a final (albeit not least) difference between what 'should be' and actual reality also needs to be stressed. While the medical and pharmacological literature (and culture) recommends the promotion of patient participation because of the value of their subjective viewpoint in the specific evaluation of quality of care and life, the

same does not happen in the PV literature (15-18). Two 'narrative' texts concerning the particularly controversial sector of psychoactive drugs represent quite interesting and original exceptions to this rule (19, 20).

A description of the history of patient populations emphasises the importance and the feasibility of widening the domain of PV competence and techniques beyond strictly clinical-pharmacological and regulatory objectives. Transferring this very innovative paradigm of research and language into current practice, however, is far from easy. Qualitative methodologies applied with formal controlled techniques (see the whole spectrum of interviews and questionnaires) are undoubtedly interesting, albeit reductive, in terms of the wide applicability. An overall evaluation of their role in the generation of innovative and representative knowledge demonstrates their limits, and explains why they can hardly be recommended as an essential element at the regulatory level (21).

1.3 Why does pharmacovigilance need a broader scenario?

The implications of what has been said so far can be summarised in a statement that can be assumed to be widely shared, at least conceptually, but that is easily disregarded in clinical pharmacology and drug epidemiology, and even more so in PV: drugs (and their use) cannot be considered primarily 'objects' to be studied *per se*, but rather as 'tracers' of health needs and policies, prescribing attitudes, and market exigencies; i.e., of the way medicine and public health goals are perceived and pursued in society.

1.3.1 The 'object' drug.

This approach might be deemed 'classical', although it is far from being widely accepted (22,23):

a) a drug (or, better still, all the strategies that have drugs as protagonists) cannot be understood, studied or interpreted at the time of registration as a product-tool-variable *per se*. All of the most important components of the scientific profile of a drug, from pharmaceutics to genomics, must be considered within the context of care;

b) the drug is a 'tracer' of a concept of medicine and public health;

c) any evaluation technique or strategy strictly centred on drugs is doomed to provide not only partial, but also misleading, information, insofar as these tend to view the context of the drug use as a secondary variable that is unnecessary for knowledge, understanding and decision-making, but is at most useful for minor adjustments to the clinical use;

d) the study and evaluation of drug 'effects' must therefore inevitably include sizes and methods that are at risk of jeopardising unbiased, 'objective' estimates and measures, to which legislative decisions are usually connected;

e) this challenge (both in terms of methodology and practice) is undoubtedly a difficult one, but it cannot be avoided when studying population medicine. In any case, it is the only perspective that can be adopted when the problem is not just the B/R clinical-pharmacological profile, but also its relevance in terms of public health (which is the mandatory context of PV). Table 1.2 gives very simple model scenarios that provide a concrete basis to assertions that might appear merely theoretical.

A review of PV in the current context must therefore refer to the more general reality of medicine, to assess whether, and to what extent, specific criteria can be drawn up to develop non-drug-centred PV.

1.3.2 The most rigorous evaluation has greater degrees of freedom.

The decade from 1980 to 1990 can now be looked at as the time of experimentation and consolidation of the methodology and practice of the production of "controlled evidence". Large population trials (which were developed and managed by independent groups) and multicentre, multinational networks radically change the scenario of experimental evaluation; with a substantial transformation of the 'benefit' component of the B/R ratio, both because efficacy measures were increasingly represented by hard endpoints with clear relevance in terms of public health, and because events more directly classifiable as safety evaluation criteria already began to be available in phase III trials (traditionally and normatively defined as those reserved for clinical efficacy). The case of the comparative evaluation of the safety profile of thrombolytics obtained in clinical trials on the basis of systemic and/or cardiovascular haemorrhagic complications can be taken as a model of this (24-28).

The decade from 1980 to 1990 can be further characterised as one of the periods with less legislative activity, and more independent scientific production; the cardiovascular field being the most exemplary and high-impact area in the light of its immediate results, particularly in the acute phase of myocardial infarction. It should be stressed, however, that the results obtained did not encourage attention to the participatory (or community oriented) aspects of the management-evaluation of therapeutic choices. Drug effects without any

consideration of the context of their use become the almost exclusive tracers of the overall yield of medical interventions.

However, by the end of the 1980's, and for very different, almost opposite reasons, society and individuals acquired protagonistic roles in two crucial areas that closely link the evolution of the knowledge and roles within medicine with some deeper value of reference categories within society:

a) on the one hand, there was the participation of women in deciding the content and priority of research in areas concerning their lives, particularly in the fields of breast cancer, prenatal diagnosis, and hormone replacement treatment (29-31);
b) on the other hand, there was the role assumed by the gay communities in claiming their right to be 'subjects/ promoters' of experimental appraisals of therapies for AIDS, the disease which produced a profound crisis in the credibility and self-esteem of medicine (32,33).

This is clearly not the place for a detailed history of these complex areas. It should however be emphasised that methodologies and norms are forced to be flexible to the point of changing radically when the value perception by society becomes visible and actively interacts, even in the early phases of decision-making processes that are normally delegated to technical and institutional subjects.

1.3.3 The evolution of the context and objectives of pharmacovigilance.

The experimentation with autonomy and independence in clinical-epidemiological research that took place during the 1980's would soon come into conflict during the strongly controversial and contradictory period of the 1990's, which reflected the deep evolution that

took place in the economics of the health sector (and, as a result, in politics and culture), and which adopted as a 'logo' the rigorously non-scientific but strongly suggestive term of 'globalisation'.

The 'facts' summarised in Table 1.3 are a minimal but necessary guide to keep in mind as a lexicon of terms, concepts and personnel that are also a part of PV.

Table 1.3 - *'Global' evolution that substantially change the operative-cultural context of pharmacovigilance.*

Year	Description
1990-92	The normative structure to register drugs in the three major market areas (USA, Europe, Japan) is defined through Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH).
1993	Twenty years after A. Cochrane's Effectiveness and Efficiency (34), the Cochrane Collaboration resumes and formalises the need to provide the choices of the medical interventions available on the world market with a basis of scientific evidence that derives from methodologically sound experimentation and is periodically and systematically reviewed through meta-analyses (evidence-based medicine).
1994	As a mandatory reference framework for the circulation of market goods, the World Trade Organisation (WTO) is established, and is also given competence over medical products; i.e. mainly drugs, but generally all within the health services that has the characteristics to be deemed a 'product'.
1996	The report on the Global Burden of Disease prepared by the World Bank and accepted and signed by the WHO is proposed as a reference criterion to decide priorities for investment, research, and planning world-wide, regardless of the degree of health care development and of political-economical autonomy of the countries.

Year	Description
End of 1990's to 2000	The macro-political framework (from wars to forced political and economical migration, to 'terrorism') progressively substitutes the policies of universal rights promotion (including access to health resources such as drugs), with policies of protection-security defence (including the protection of the interests of those producing or possessing economic goods, of which patents and competitiveness in the drug area are both the expression and the symbol).

The process that highlights the close relationships between 'macro' and regional-local levels is a very complex and articulated institutional, cultural and economical process:

- The formulation of a common normative framework is overdue, particularly because it involves goods that directly influence people's life and health. Efficacy is ensured more effectively by following rules that promote, protect and control data reliability and accountability. However, the ambivalence of legislation (GCP-ICH) that focusses entirely on the 'products' to be registered is obvious: the research objects are the drugs, rather than the problems to be solved *also* through these drugs. Parallel to this legislation, a more general framework of investment that has reduced public contributions has developed, hence reducing the autonomy of research groups that are non-dependent on 'commercial' investments, the primary objectives of which are obviously the creation and fruition of market areas, rather than the research into unmet public health needs.

- Evidence-based medicine constituted a substantial step forward towards the structuring of a widespread culture of responsibility beyond the results of individual studies, by favouring interventions where efficacy is systematically and cumulatively assessed.

Nonetheless, the risk of dependence of this comprehensive knowledge on the availability of individual results derived from clinical trials mainly promoted and carried out for drug registration is immediately apparent. Furthermore, although the evidence is based on 'experimental' efficacy, the claim is for it to turn into guidelines for long-term practice in the very heterogeneous contexts of care and populations only very partially represented in clinical trials. In the consequent B/R ratio, the R component is inevitably and concretely given a secondary place (particularly if R is not just the drug-related SARs). It is well known that while procedural rules were being introduced, conflicts of interest started to increase. Notwithstanding the reports, the scandals, and all of the initiatives undertaken to check for conflicts of interest through the authors' 'declarations', the situation does not appear to have improved over the years. Some of the most dramatic episodes of SARs belong to the epoch of perfect procedural control over the clinical trials.

What happened for Coxib (35,36), antidepressants (37), and antipsychotics (38-41) (to quote the most widely known cases) shows that conflicts of interest have indeed involved regulatory agencies quite heavily, due to the more or less direct role of concealing information on the B/R profile of drugs intended for wide use, with important epidemiological and public health implications (42-48).

- It is highly significant that an independent organisation such as the International Society of Drug Bulletins (ISDB), started in the mid-1980's to provide information on prescriptions (i.e. on the last phase of the development and introduction of drugs in clinical practice), whereby it had to focus its priorities of attention and intervention on:

a) the 'new' drugs, which do not represent in fact 'new' anxieties to unmet needs, and can be considered therefore as severe adverse events, as they profoundly damage rational prescribing (49);

b) the need for more diversified PV, involving both prescribers and patients in an innovative way (50);

c) the 'institutional' opposition of the regulatory agencies (particularly in Europe) to substantial, preventative 'accountability', i.e. not granted in retrospect, or one by one (51,52).

- The global context chronologically described in Table 1.3 adequately defines the current situation with respect to the PV policy, which is clearly very different from that described in Section 1.2. Drug-centred PV that insists on procedure formality (until the last proposal by the EMA) appears bound to remain marginal with respect to the need of real prevention-protection from unsafe strategies (52,53). Obviously, PV must be concerned with individual drugs, but it cannot choose not to consider the questions simultaneously posed to drug policies and public health.

1.4 Towards an integration of participatory epidemiology in pharmacovigilance.

Far from being rhetorical, the discussion is quite technical. It refers to the essay by Cochrane quoted above (34). Cochrane posed this in terms that are only linguistically

different, with reference to even more ancient roots, to coincide with the very beginning of the culture and methodology that had defined drug evaluation as one of the chapters of epidemiology and public health (54).

Randomised controlled trials (RCTs) were intended as an instrument that would speed up the production of reliable knowledge for relevant public health needs for which an intervention is potentially available (be it a drug, a vaccine, or a technology) and that could modify the natural history of the condition. A possible risk is accepted if there is an improvement in the right to life and health of the individuals and populations with the condition. In this respect, it is less a technique (very clever and not too technological) and far more an exercise of accountability and communication that puts epidemiology in close contact with the reality of individuals and populations:

- By unequivocally declaring a shared lack of knowledge between experts and citizens;
- By expressing explicit equity criteria according to which drugs, vaccines and technologies are distributed within populations that have specific needs;
- By committing itself to making known not just the results, but also why and how the results might or might not be translated into common good that will be accessible to all of the potential recipients. Cochrane's 'effectiveness' synthesises this overall vision in a public health perspective, which sums up the knowledge with respect to efficacy, safety, efficiency and appropriateness.
- The long-term cohort of women exposed to oral contraception followed up by British General Practitioners (GPs) is a non-randomised translation of the same objectives of attributable efficacy plus safety (55);

- The (as yet not computerised) database record-linkage of GPs and specialists was part of the same perspective, concentrating on non-cardiological SARs of a drug like practolol (a true prodigy of cardiovascular efficacy) (56,57).

The many diverse PV strategies mentioned in Section 1.2 are therefore innovative also because they ensure the presence of three characteristics:

a) they indicate the need for high methodological flexibility;

b) in different ways, they all envisage explicit participation of the more directly involved actors, who, beyond just feeling part of an *ad-hoc* study, begin to include safety surveillance among their normal duties of responsibility and accountability in evaluating if, and to what extent, their interventions match expected results, and therefore they accept a commitment to patients in terms of efficacy and safety (this should also be the perspective of techniques and strategies such as spontaneous reporting and restricted release monitoring);

c) they document the fact that it is both expected and possible that all of the actors as well as all of the sources of information involved will have a role, to guarantee the full understanding (i.e. not just drug-centred) of the effects of drugs and technology in the management of problems, discomfort and diseases that complement one another.

In the times and contexts (see Section 1.3 and Table 1.3) that have seen drugs (and technologies) gradually turning not just into a resource within everyday life, but also into protagonist-goods within a market defining and influencing choices, priorities and values of medicine and public health, PV can only follow the same path.

'Risk management' surveillance (prevention + early detection + adequate information management + alternative interventions) has assumed more general terms and features than those defined in the SAR reporting procedures: the risk of improper use; useless indications; non-accessibility to due/ recommended treatment (owing to lack of availability in contexts with scarce resources or to inadequate information, rather than to non-compliance of the patients); risk of disease mongering; excessive induced use of treatments that promise a lot while producing very little.

Table 1.4 is a non-comprehensive reminder/ example of the concreteness of this proposal for the widening of the definition of SARs. What has been argued so far, and the examples provided, should have clarified that in this perspective, responsible and effective surveillance is intended as the overall surveillance of medical interventions to ensure the rights of individuals and populations to be informed, with the right to an opinion in their own care process.

Table 1.4 – *Questions that require pharmacovigilance definitions to be forgotten, and to focus on epidemiology.*

It is widely recognised that the almost exclusive focus of PV is on individual drugs and on alarm-raising SARs. Attention should preferably be switched to the epidemiology of the problems/ populations, to broaden the information from direct drug effects to the outcomes of interventions/ strategies where the overall B/R yield of drugs is one of the variables.
What is the B/R profile of antidepressant drugs, where the registered indications include a spectrum of heterogeneous diagnoses that coincide with even less-well-defined populations and are based on surrogate end-points that do not reflect the life of the people involved? Are we measuring placebo B/R profiles, or are we producing a 'disease mongering' process (i.e. a culturally iatrogenic, epidemiologically, relevant side-effect)?

Coxib was a great marketing event, with their promise of lower gastrotoxicity, which soon became a model case of 'global' misconduct with the failure leading to their withdrawal, and a success story of problem-oriented epidemiology. Nobody apparently felt the ARs of the absence of their 'benefit'. What is the epidemiology of the unmet needs of the huge populations of chronic suffers of osteoarthritis?
The new generation of oncological drugs are most often approved and used on the basis of minimal or doubtful benefit, excessive costs, and 'standard' biological and quality-of-life related toxicity. What could/ should be the object of pertinent PV? What is the trade-off between hope (the B), and disillusion (the R)? What is the impact of the (cultural, methodological, economic) R of concentrating research and care resources and expectations on pharmacological effects, and less on the overall epidemiology of care of oncological patients?

Patient-based PV is not simply an exercise that involves the patients through questionnaires or focus groups, or more or less sophisticated qualitative techniques; these procedures (greatly developed in pilot studies) can indeed be relatively useful (58-60). Whenever they are applied as 'further' techniques but they remain substantially drug-centred, they do not go very far. They might be cosmetically instrumental within clinical-procedural PV, but might provide no answers in terms of value and sense; i.e. the questions currently posed to medicine by a society in which citizens rights, rather than the increased availability of diagnostic procedures, should be the reference category.

Figure 1.2 is an example of possible and practicable epidemiological surveillance ('starting from', rather than 'centred on', the drug) in which all of the actors have their own roles in a complementary and flexible way, to make 'safety' an expression of respect and a promotion of rights rather than a separate monitoring exercise. Obviously, this perspective makes sense only for those who believe that drugs and their management are 'tracers' of

medicine's legitimacy, and that medicine and its management are 'tracers' of a society's capability of expressing a right to life rather than just being a tool of sustainability and a development of market interests.

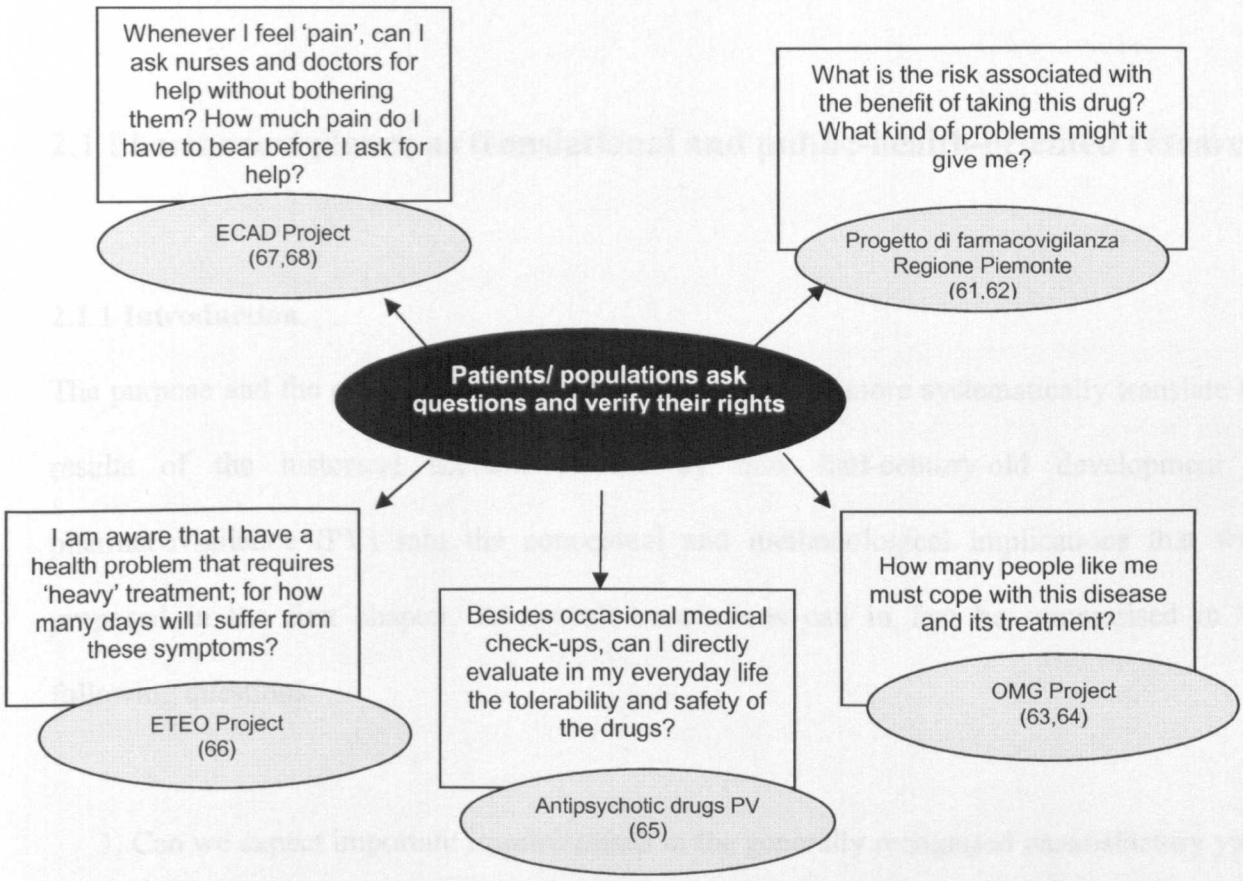

Figure 1.2: *Strategies of active involvement by citizens-patients.*

CHAPTER 2

Towards patient-centred pharmacovigilance. Methods, instruments and strategies.

2.1 Pharmacovigilance as translational and public-health-oriented research.

2.1.1 Introduction.

The purpose and the objectives of this chapter are to try to more systematically translate the results of the historical account of the by now half-century-old development of pharmacovigilance (PV) into the conceptual and methodological implications that were proposed in the first chapter. Its overall conclusions can in fact be summarised in the following questions:

1. Can we expect important improvements in the generally recognised unsatisfactory yield of regulatory-centred PV strategies via adjustments to the rules applied for drug registration and marketing?
2. Or should PV become a comprehensive public-health-oriented area of permanent research that aims to systematically monitor the roles of (pharmacological and non-pharmacological) interventions in the practice of medicine, and in the life of populations?

The even more recent regulations and recommendations of the regulatory agencies (69-71) appear to be oriented along the first of these two scenarios. This has as the almost exclusive protagonists on one side the (drugs and devices) producers, and on the other side the regulatory bodies. The analysis that has guided the historical framework proposed in Chapter 1 goes clearly in the direction of the second scenario, which is the hypothesis of this study. It is clear that this approach implies a re-formulation of PV, less as a branch of pharmacoepidemiology and more as a component of epidemiology and public health. The main targets and terms of reference of PV are not one or the other drug, but the problems/ diseases where their management and care include certainly drugs, interventions and devices, and where the results of variables and actors are the key determinants of the broader choices and evaluations that define the profile of efficacy, safety, economic sustainability, and patient satisfaction of interventional strategies.

While, by definition, all of the techniques that have been developed and applied in PV retain their specific roles, it is more important to focus on:

- First, the broader framework where they are used (2.1.1);
- Then, the critical role of epidemiologically oriented databases, in their general aspects (2.1.2);
- And, their concrete applicability in the context of the National Health System of Italy, where the model scenarios of this study have been developed (2.1.3);
- Finally, conclude with a longer discussion of the methods and strategies that can provide the original development of citizen-patients-oriented PV (2.2).

2.1.2 Key words for patient-oriented pharmacovigilance.

Table 2.1 summarises the conceptual and methodological scenarios that should be considered as integral components of PV, and that are supportive of the hypothesis put forward in the last of the five points. We proposed to apply the term '*translational*' to PV (which has become fashionable over the last few years, mainly at the interface between basic and clinical research), to identify the need of a more effective continuity across the 'specific' results of the various phases of scientific discoveries, to assess their overall yield in terms of health improvements. This is not an all-too-easy adoption of a suggestive new qualification for an old discipline. It is the rigorous consequence of the steps that are proposed in the first four points, which deserve a brief explanation. The sequence from efficacy to effectiveness, to outcome, to public health, to citizen-patients rights (point 1) has become more and more a dominant paradigm in the most recent literature, that had also documented the discussion that has accompanied (last but not least) the re-definition of the health policy of the USA (72-77), but which are also at the centre of the debates and reforms in the health systems in Europe (78) and globally (79).

Table 2.1 - *From a formal control of drug safety to participatory understanding of the role of a drug in medicine and society.*

1	Efficacy → Effectiveness → Outcomes → Public health → Patients rights
2	Epidemiologically intensive use of administrative databases, with cross-disciplinary record linkage to account for life context-related variables, and nested *ad-hoc* studies.
3	Systematic integration of:

	-quantitative and qualitative data, approaches, tools; -objectively defined variables and perceptions of citizens-patients
4	The great intrinsic risk of PV is to pretend to apply the same methodologies to problems/ therapies/ populations which coincide with and represent different 'universes'
5	PV not as a phase of drug development, but the permanent translational interface between 'interventions' (drugs and devices) and care.

The topic has already been touched upon in Chapter 1, and so it does not need to be discussed again here. What matters is to stress the specific relevance for PV, which, in principle, has its focus and goal on the last of the terms of the sequence: the purpose of PV is primarily to assure citizen-patients rights to safety (the old principle of medicine is first to 'do no harm'). It has become increasingly clear however that 'direct harm' by a specific drug or intervention is not an independent variable. It is one of the components of the appropriate use of drugs, which cannot be assured by a control, which does not take into account the full chain of decisions and context, and which determines the conditions of 'exposure' (or no exposure: as direct harm is also a lack of appropriate accessibility to a treatment, and not only in deprived health systems) to an intervention. Only the contexts of care that through public health policies, creates the institutional, cultural, and organisational conditions where individual and collective rights to health measures are protective also of the safety. A PV which is not focused, comprehensively, on the outcomes of interventions cannot discriminate between the usefulness, the efficacy and the safety components of the interventions. Any discontinuity across the key words of point 1 breaks the possibility of including the

interventions (which are definitely one of, if not the main, expressions of medicine in its interaction with the health of individuals and populations) among the variables which 'make the difference'.

The framework of point 1 is the key passage for the transformation of PV from a branch of pharmacology into a principal expression of epidemiology and public health.

The methodological implications of this basic approach are straight-forward and are set out in points 2 and 3, which will be further developed later on. They simply indicate that all the tools, sources and methodologies that are part of the epidemiological surveillance of the health needs and outcomes are normal resources of PV, with an accentuation of their reciprocal and flexible complementarity. The key caveat is highlighted in point 4: the separateness of the objectives and of the results expected from registration of a drug has created a strange situation, which sees PV as an activity-discipline which prefers, and recommends, standard methodologies and rigid criteria for producing 'significant' information, instead of being focused on the problems, diseases and populations for which a new drug has to represent an answer. Such an approach could certainly be seen as a more practicable strategy for defining the commitments of producers of drugs/devices as it allows the conclusion of the phases of the registration process: it is clear however (and the scenarios briefly mentioned in chapter 1 were a good demonstration) that classical PV remains, in reality, on one side a marginal and often misleading source of relevant information, and on the other side it is bound to reflect the controversial relationships between private-market interests and priorities and those of the real individuals and the need of guaranteeing-developing a public-health-oriented and participatory culture of the society. The translational character and vocation of PV appears in this sense to be specifically important. In each area of

medicine, a policy of PV must adapt with methodological flexibility to the specific needs of the populations and of the problems that are involved. It cannot be considered a discipline that produces specialised reports to be used principally for regulatory purposes. Among its goals, the ability to produce and communicate results in a suitable language and with the participation of all of those who are involved in the process of care and health education must be seen not as an optional 'plus', but as a condition of transparency, and therefore of legitimacy.

2.1.3 The critical role of databases that describe and monitor the real-life and care of a population.

The potential, and often original, role of so-called administrative databases was recognised very early in the area of epidemiology and public health (especially as soon as the first computerised systems of data collection become available). They thus represented a mandatory tool for health systems, that were aimed at providing both informed planning of their activities, and a timely capacity for the assessment of met and unmet needs of a population. Table 2.2 provides a very simplified reminder of the population databases that have contributed substantially to the history of epidemiology (as well as of PV), and to the creation of a culture of public health.

The reasons for the importance of these databases for the documentation of the possibility and the yield of a continuity across the terms listed under point 1 of Table 2.1 are well recognised and have been commented and stressed over and again.

Table 2.2 - *Main 'historical' population databases.*

Database	Description
Oxford Record Linkage Study (Great Britain)	Acheson and colleagues started to use record linkage in 1960, to create an integrated file of health data for a community in which the main events that occur are not only recorded, but are also brought together in such a way as to allow both cross-sectional and longitudinal linkage of events (80).
Saskatchewan Database (Canada)	A large amount of health care information collected over a number of years: prescription data, outpatient and hospital diagnostic information, cancer and vital statistics, and services such as mental health, chronic care, children's dental care, and alcohol and drug abuse services (81, 82).
Norwegian Prescription Database (NorPD)	The Norwegian Institute of Public Health data of all dispensed prescriptions: they could be linked (and have been linked) to many other databases, because each prescription is identified by a unique person identifier. The Norwegian Patient Register is based on the information in the electronic discharge register of the hospitals (83, 84).
Ostergötland County (Sweden)	Data on hospital care and primary healthcare (PHC) have been entered in a diagnosis-related administrative database since 1999 (85).
British United Provident Association (BUPA)	BUPA was established in 1947, when 17 British provident associations joined together to provide healthcare for the general public. It was founded as a not-for-profit provident organization, to meet the needs of those wanting something more than the National Health Service (established in 1948) system in Britain offered. Over the years, it has diversified away from its core health insurance business and is now an internationally established health insurance and care company (86).

Database	Description
Kaiser Permanente	This is an integrated managed care organisation based in Oakland, California, USA. Kaiser Permanente evolved from industrial health care programmes for construction, shipyard, and steel mill workers for the Kaiser industrial companies during the late 1930s and 1940s. It was opened to public enrollment in October 1945. Now it is a national leader in the implementation of integrated electronic health records. Physicians and specialists, nurses, pharmacists, and laboratory technologists can enter and retrieve data using a computer-based patient record cradled in security, at any point of the service from the medical office to the hospital setting. Through KP Health Connect, the member's primary care physician and the clinicians involved in the total health care of the member can connect to information on therapies, interventions and preventive care to improve health and the quality of life (87).

They are simply recalled here to make them more evidently linked to their implications for PV.

- They provide the true denominators of the populations that are exposed to the risks of their diseases, and of the related interventions. While the populations included in trials where interventions are tested are, by definition, selected and limited (numerically, and for the length of observations), the databases that document what happens to population (covered by insurance, or the health system) do not foresee, by definition, exclusion criteria, and follow the individuals over longer periods of time.

- The linkage of various databases allows the inclusion and analysis of non-medical variables (such as contexts and conditions of life) that are often the key determinants in the exposure and of the reactions to diseases, risks, and [quality of] care.
- When, and if, needed, the basic information that is collected routinely and with no additional costs can be integrated with *ad-hoc* supplementary focused data, which helps to define the hypothesis of analysis well.
- The substantial concordance of the basic criteria which define databases of different origins allows an easier comparison of the roles and impacts of the key variables.
- The main outcome measures of morbidity and mortality are included (either directly, or through linkages), so that outcomes are more easily associated and analysed in close and flexible connection with exposure.
- The increasing and substantially limitless capacity of the computerised systems of data collection, monitoring and analysis have made the systems more and more robust. On the other hand, the intensive use of the databases for different purposes has allowed the development of statistical techniques and approaches that allow reasonably effective and reliable control of the main confounders.
- While the limits are obvious (e.g. a lack of detailed clinical data) and well recognised, there is no doubt that the combination of the various databases has become a dominant component of epidemiology and public health.

The literature that has critically explored all of the above aspects is enormous and cannot be mentioned, except through model references (88-95).

It is interesting to note that administrative databases have been substantially less used for drug epidemiology, and even less for the purpose of PV, although (as recalled in Table 2.3) some historical cases have documented their yield. The main reason can be seen as a conceptual barrier. Drug epidemiology (based on administrative databases) has been considered far more as a task of description of the variability of the practices, than as a way of exploring the link of drug exposure to outcomes (96-100).

Table 2.3 - *Historical experiences of pharmacovigilance based on the flexible application of linkage of different types of databases.*

Drugs/Databases	Description
Practolol	Oculomaculocutaneous syndrome was defined after recognising different tissue damage produced by practolol (101). Lesions in the ears (Wright, 1975), kidneys (Farr 1975), liver (Brown1978), lungs (Marshall, 1977) and peritoneum (Brown, 1974) were all reported; a lupus-like syndrome has also been attributed to practolol (Raftery & Denman, 1973).
Boston Collaborative Drug Surveillance Programme (BCDSP)	The BCDSP (102) was established in 1966. It was the first group to conduct formal epidemiologic research to quantify the potential adverse effects of prescription drugs using in-hospital monitoring, and it had a pioneering role in the development and application of methods in drug epidemiology. Among the many reports published, some examples are cited: • Adverse reactions to intravenous diazepam (103); • Excess of amphicillin rashes associated with allopurinol or hyperuricemia (104);

Drugs/Databases	Description
	• Allopurinol and cytotoxic drugs. Interactions in relation to bone marrow depression (105).
Spironolactone	A population-based study by Juurlink et al. (106) used linkage of prescriptions and hospitalisation archives to compare the management and outcome of heart failure before and after the introduction of spironolactone. There was no significant decrease in the rate of readmission for heart failure; on the contrary, there was a substantial increased in the rate of hospitalisation for hyperkalemia and the associated mortality was documented.
Treatment for Transient Ischaemic Attack (TIA) or Minor Stroke	A prospective study nested within a rigorous population incidence study of all patients with TIA or stroke was carried out by Rothwell et al. (107, 108), to determine the association between more rapid treatment and outcomes in patients with TIA or minor stroke. The results of this study documented that early initiation of existing treatments was associated with an 80% relative reduction in the risk of early recurrent stroke.
Antithrombotic Treatments in Atrial Fibrillation	Monte et al. (109) carried out an Italian population-based study to assess the use of antithrombotic treatment (ATT) after hospitalisation with atrial fibrillation (AF). On the basis of record linkage, they demonstrated that ATT was underused, even though exposure was associated with improved survival among elderly high-risk patients in community hospitals with AF.

The case of the abuse of observational studies (derived also from administrative databases) in affirming causal associations, such as in the model case of hormonal

replacement therapies (110), has certainly been one of the discomforting reasons to trust the possibility of treating drug exposure as a 'hard' epidemiological variable.

A sound epidemiological approach to analysis of administrative data was, however, shown early on to be reliable protection from the risk of overinterpreting associations in terms of causality (111, 112). Two main methodological contributions (at the beginning and at the end of the BCDSP experience presented the solid foundations to causality assessment studies) provided robust methodological background for reliable use of non-experimental design for the exploration of causal relationships focused on safety issues.

Far from disproving the relevance of using routinely available data on the case histories of unselected, and therefore specifically representative, populations, the criticisms to their misdirected use sharpened the interest and the intelligence in considering drug exposure as it is in reality: a variable that incorporates all the bias that occurs in real life and care, and which therefore must be analysed (and corrected for) as the product of the (subjective vs informed) medical decisions, the patient's preferences and compliance, and the uncertainty or indefinition of a diagnosis (113, 114).

The objective and the specific contribution of comprehensive PV in monitoring and assessing the overall benefit, risk, and acceptability profile of therapies also through databases correspond to the ability to provide information on what might be the outcomes of exposing populations to a mix of the rational and less rational, of carefully monitored and of carelessly prescribed therapies, and of patients who adhere to and do not participate in the therapeutic plans. Here also, the caveat of point 4 in Table 2.1 is valid: databases are not homogeneous, nor are they the way drug that exposure must be analysed according to rigid standard criteria (except those related to the material quality of the data) (113, 114). A clear and specific

knowledge of the clinical-epidemiological problems that are analysed, and of the specific bias to be considered for one of the other populations and their context of care, are a prerequisite: no sophisticated sensitivity analysis can correct for a lack of plausibility of the hypothesis, or of the intelligence of the research protocol.

Far from being simply a cheaper and readily available resource, the databases (and the related and linked automatic or *ad-hoc* integrations recalled above) must be considered a privileged and powerful tool:

- to generate and to test hypotheses;
- to quantify and qualify the robustness of these hypotheses across different population strata exposed to specific patterns of drug use;
- to identify subgroups at specific risk, so that *ad-hoc* monitoring and assessment strategies can be activated with well-tailored protocols;
- to provide specifically original inputs on the roles of the quality of the structures that deliver health interventions in determining the outcomes of individuals and populations.

Due to their fundamental orientation and goal to document the interactions between health needs (as they are reflected and managed through health-care delivery), and the outcomes that are achieved, the databases allow us to ask the questions, and to propose some answers of classical PV. At the same time, they remind us that the care issue is not "what safety problem is associated with this drug", but "how is the history of this disease in this

population influenced and modified by the fact that drugs-devices-based interventions are, or are not, part of the epidemiological variables that determine the outcome".

2.2 Administrative databases in the real context of the Italian National Health Systems.

2.2.1 Main databases characteristics.

Secondary data in research are data that have not been collected with a specific research purpose, such as: administrative databases (health care use archives), i.e. prescription databases, hospital discharge records, and civil registries are among the most used in epidemiology (115).

In Italy, the administrative data results from the health care delivery, and the reimbursing for services (as dispensed drugs or other health-care intervention) by the Italian National Health System (NHS).

The NHS, organised through the Local Health Authorities (LHAs), manages all of the health services, including hospital care, while Hospital Trusts provide tertiary and highly specialised care. There is no separation between purchasers and providers: LHAs provide health services according to the general national law regulating the NHS. In Italy, around 90% of the available drugs can be reimbursed through the NHS (although in some Regions a quota, known as a *ticket*, is paid by patients, also for drugs that are reimbursed), after collecting and sending all of the prescriptions to the LHA that are dispensed in the community pharmacists ad are covered by NHS.

Three computerised administrative databases that are routinely available in each LHA are:

- prescription databases that contain community prescriptions reimbursed by the NHS, with information on the type and quantity of dispensed drug (generic and brand names) and the dispensing date. Drug are coded according to the Anatomical Therapeutic Chemical (ATC) Classification (116), with patient information (gender, name, "sanitaria" and fiscal code) and prescriber identification number;
- Hospital Discharge Records, with information of the main diagnosis, and up to 5 secondary coexisting conditions, the main procedures performed, the dates of admission and discharge, and the indicator of hospital mortality, and patient information (gender, name, "sanitaria" and fiscal code). All diagnoses are coded according to the International Classification of Disease, Ninth Revision, ICD-9 CM (117);
- population registry with patient-demographic information, such as gender, date of birth, fiscal and "sanitaria" code, as subject identifiers of all patients of a LHA.

These databases are used mainly for reimbursements, even though they represent an important tool for epidemiological studies. The most important advantages that derive from the use of administrative databases in epidemiology are that they are readily available; computer readable; cover a large well-defined population, and sometimes encompass entire regional populations. On the other hand, they also have some limitations: their source documents contain the minimum amount of information required to perform the relevant administrative function. In particular there is a lack of important information like:

- the clinical profile of the patient (baseline pathology and comorbidities);

- the reasons for and the duration of the prescribed drugs;

These data need to be accessed by a methodological strategy of the combination of the different variables present in the archives.

For these reasons, 'prescribed drugs' are considered as indicators of specific clinical conditions, that alone or in combination with other data (such as patient age, chronic or occasional use and specific hospitalisation) can be used to identify specific diseases.

On each prescription for a drug reimbursed by the NHS, it is possible to prescribe two different drugs and a maximum of two boxes (of the same or different drugs). For particular chronic conditions (e.g. like hypertension, osteoarthritis), it is possible to prescribe 3 boxes on each prescription. The prescription does not contain the duration of the treatments, and for this reason it not possible to identify the daily dose used. The identification of 'chronic' calculation has been performed using the total number of boxes of the same drug received in a well determine period (say, 12 months): the number of boxes is a good indicator for the identification of occasional and chronic patients (118).

2.2.2 Record linkage.

Record linkage is the primary tool to integrate information derived from different sources (119-123). Linked documents can be treated as a single document for an individual or a family. Health care providers find linkage for individual patients useful, as they often need longitudinal information to get a complete picture of a patients' use of structures and services.

Record linkage has three main technical difficulties:

1. Using personal identifiers to recognise specific subjects.

2. Deciding whether discrepancies are due to input errors or to interference with other individuals' data.

3. Processing the large amount of data required for record linkage within a reasonable time.

2.2.3 Comparison between record-linkage techniques.

The choice of the most appropriate record-linkage technique depends on the quantity of information available in each of the data archives to be connected. Powerful identifiers (unique numbers, such as tax codes, NHS codes, names) can sometmes be missing: there are two possible strategies for pairing, i.e. a deterministic (euristic) or a probabilistic approach.

Deterministic record linkage techniques use a series of rules based on the exact matching of the set of characteristics (fields) that represent the identification key of an individual. The simplest and most intuitive deterministic method establishes that records from different sources are recognised as pertaining to the same subject when the entire identification key coincides.

Semi-deterministic (or stepwise) procedures belong to the same category, and are characterised by a sequence of steps through which the agreement is evaluated for a subset of identification fields. Although deterministic techniques are widely used, they have often been criticised mainly on the grounds of their doubtful ability to recognise a match in cases of uncertainty.

Probabilistic techniques were formalised by Fellegi and Sunter (124), and these assume that individual matching between identification fields is insufficient to determine the

actual pairing of two records; rather, the decision is based on both the discriminatory ability and the reliability of individual identification fields (125-127).

The record linkage process might involve matching errors that can potentially influence the results of a study (128). To date, there is a dearth of studies that have evaluated the effects of record linkage errors on the validity of epidemiological measures. The majority of the studies concern the set of identification fields that can minimiss errors of specific deterministic procedures (129-131). However, the results of these studies can hardly be generalised to different contexts than those in which they were produced. Probabilistic techniques, insofar as they are based on the characteristics of identification fields and on the quality of the data, are more promising from this point of view, as they involve a decisional process with respect to the error size deemed acceptable in the specific context of the application (132-134).

An Italian study compared record linkage techniques in different contexts, using health care databases, and evaluated the operative characteristics of a standard probabilistic technique developed for epidemiologic purposes (135).

The comparison between the performance of record linkage techniques in the four Italian centres showed that:

- the deterministic approach has the lowest sensitivity threshold and its use should be limited to situations where good quality, unique identification codes are available;
- the probabilistic approach mentioned above is comparable to that commonly used by centres adopting a manual revision of non-matched records or quality control of identification fields. Whenever this is not done, the technique involves systematic errors where the direction and size are unknown.

The performance of probabilistic techniques is closely associated with the quality of the available data. The time required by the different record linkage techniques depends on the size of the databases to be matched and on the hardware used, along with the RAM and free disk space available. The probabilistic procedure is more complex and therefore requires longer execution times.

2.2.4 Application of probabilistic procedures: clustering-linkage validation.

Often, administrative databases refer to events rather than to individuals. Whatever their nature (e.g. hospital discharges, drug prescriptions, specialist interventions, death records, tax exemptions, disease registers), administrative databases are a collection of information in which the elementary information unit (record–observation) generally consists of data concerning the patients' hospitalisation, drug prescription, and so on, rather than the patient themselves (i.e. little clinical information is reported).

Since events associated with each subject are not unique within the same database, there may well be more than one record concerning the same subject, and within each of the databases used there might be at least one record concerning the same subject. Therefore tracing back event information to the subject means grouping different records by common identification codes and allocating them to apparently homogeneous clusters.

This is in every respect a process of database partitioning, based on an equivalence relationship applied to records and defined by the 'information similarity' of the vital statistics fields: the equivalence classes thus generated represent clusters of patients.

Similarly, the clustering process can be accompanied by factorial analysis that is applied to rows (records) rather than columns (variables), in which the factors identified are

not axes of the new reduced space, but the (less dense) set of new points (cluster-patients) within it. The clustering concept is valid also for multiple databases, although generally their different natures require a synchronised, parallel and consistent application, as in this instance the objective is not just that of identifying clusters within each database, but that of comparing their differences or similarities across the different sources of information.

In other words, the integration of different databases in a centralised patient-based system requires a data linkage process beyond simple data clustering, in which the subject individuation has to be followed by the subject identification.

The latter aspect introduces significant complications to the process of tracing back from event to patient, insofar as both clustering and linkage require the definition of keys on which a grouping is formed. This involves the choice of vital statistic fields that are more appropriate to the specific situation and more likely to fulfil the objective of the study.

As different databases are often heterogeneous, in the record linkage process this can greatly reduce the vital statistics fields that are usable as join keys. If the clustering process operates in an autonomous and asynchronous manner on the available variables defined as keys within a single database, the linkage procedure can only operate synchronously on the group of fields that the databases to be linked have in common.

The set of data used for linkage is therefore smaller than that for clustering, and it might be that it involves those variables that are qualitatively less reliable, as well as potentially more affected by errors, which can eventually fatally hinder the joint procedure. For this reason, the use of a reference database, such as the NHS list, might be crucial. Even in the case of clustering, a reference database substantially improves the quality and completeness of the data due to the possibility of correcting and integrating information by

'recognising' the patient and completing the missing vital statistics data that can be used as linkage keys. The use of a reference database therefore guarantees to some extent data validation, and from a methodological point of view, this makes linkage and clustering largely equivalent, insofar as patient identification allows clustering to be carried out asynchronously in individual databases and then to perform data linkage through a simple joint procedure of the information pertaining to the same patient.

2.2.5 An advanced programme for automatic computation: the ReClust routine.

The ReClust routine implements an algorithm in the SAS language for probabilistic record linkage of different administrative databases (e.g. hospital discharge forms, drug prescriptions, death records). Through iterative sequential steps, it groups records (e.g. hospitalisations, drugs) according to correspondence and matching of several aggregation keys, until it identifies record clusters (subjects-patients) that are homogeneous in terms of the content of the keys.

Depending on the availability of reference databases for validation (the NHS list), the routine can proceed asynchronously or synchronously, so distinguishing between or unifying the cluster phases of each database included in the linkage procedure, until an absolute or a relative identification of the cluster is reached, and a cluster code (patient code) is assigned to each record. This allows the identification of the subject in each database; furthermore, it becomes the linkage key to integrate different information sources, both longitudinally and transversally. Its uniqueness preserves absolute anonymity of the subjects involved and full respect of their privacy. For further details on the ReClust routine, please refer to the Consorzio Mario Negri Sud website (136).

2.3 Citizen-patients as subjects and protagonists of pharmacovigilance.

2.3.1 General framework.

The increasing importance of the 'point of view' of citizen-patients in society (and consequently in health care) is well established, at least in terms of the declaration of principles, and repeated agreements and recommendations on the needs of and criteria for participation (137).

Both in society and in health care, however, it is similarly recognised that there is a substantial dissociation between what should be done and what is being done in all matters that coincide and/or are borderline with the areas of interplay between the increasing pressures of a market-driven, and therefore directed, society, and the respect for personal (collective and individual) rights (138).

The medical literature documents "beyond any reasonable doubts" that patient-centred and qualitatively well-focused studies are regularly and frequently reported, but they fail to produce solid or respected enough evidence to become part of the general cultural background, and even less so for current practices. The case of quality of life instruments and results is possibly paradigmatic: the prognostic yield of these instruments on the hard outcomes of patients and populations can be easily qualified as a piece of evidence-based medicine (at least as solid as fashionable biomarkers), but they are not included nor considered as part of the recommended practices (139,140). We are facing something that is very deeply rooted in the [self]-identity of medical sciences: conceptually and methodologically, their interest for persons (and for their histories) is mandatorily mediated

by their competence and outlook on diseases. Individuals and populations are therefore implicitly, and therefore even more profoundly, objects of attention. Their re-conversion into subjects, with 'normal' i.e. personal, not 'patients' rights, is a separate step and a duty that is easy (and 'politically correct') to affirm, but which remains in the area of what is intrinsically optional, as "if and when it is needed". The procedures of informed consent are a model of this process: they have become the most bureaucratic, and least transparent, component of clinical experimentation, where the sharing of common ignorance between health-care professionals and the patients should create the ideal condition for dialogue, in view of the collaboration needed to look for the answer (141-143).

This possibly too broad and long introduction is not a deviation from the interests of this chapter. The issues that have been briefly mentioned coincide with problems that are central for a comprehensive approach to PV:

- by definition, the experience of side effects/ adverse events are a mix of subjective sensitivities, perceptions, and recognitions, and of objective signs and symptoms;
- because of the prevalent focusing of PV on drugs and on their clinical safety profile, the documentation of 'hard' manifestations has received almost exclusive attention in the various reporting systems;
- the narrative-subjective experiences have been only marginally (and most often with a high degree of controversy) admitted into the regulatory considerations;
- the integration of qualitative data and histories into the mainly quantitatively oriented epidemiology produced in the various phases of drug development and monitoring is

a recommended practice, which, however, is only occasionally translated into practice;

- the points that follow aim to provide an essential background of the methodologically issues and model experiences that appear more specifically relevant for the general objectives of the present project.

2.3.2 The broad framework of citizen-patients participation in healthcare.

Table 2.4 defines some of the main steps that have contributed to the conceptual, methodological, and institutional development, and that have led to the recognition of citizen-patients as autonomous, and knowledge producing, subjects in public-health issues and settings.

Table 2.4 - *The main steps in the recognition of citizen autonomy.*

Document	Brief description
1978 *Alma-Ata Declaration (144)*	This is the first important document in which it was established that people have the right and duty to participate individually and collectively in the planning and implementation of their health care.
1986 *Ottawa Charter for Health Promotion (145)*	The WHO organised the First International Conference on Health Promotion, with which it wanted to give a response to growing expectations for a new public health movement around the world. Health promotion action aimed at reducing differences in health status, ensuring equal opportunities and resources to enable all people to achieve their fullest health potential.

Document	Brief description
2001 *Expert Patient (146)*	The Department of Health in Great Britain published "Involving patients and the public in the health care", followed by the document "The expert patient: a new approach to chronic disease management in the 21st century" in which the Chief Medical Officer for England first introduced the term *expert patient*, which was soon after picked up and used widely.
2005 *Bangkok Charter for Health Promotion in a Globalised World (147)*	The participants at the Conference forcefully call on Member States of WHO to move to policies and partnerships for actions to address the determinants of health in a globalised world by reaching out to people, groups and organisations.

It is easy to understand from the substantial repetition of the same recommendations that it has not been, nor is it, a linear story. On the contrary (and in parallel with what has happened in the 'global' society in the area of human and civil rights), a participatory approach has been most often confined (with the due exceptions) to the role of providing an attractive public image, which could make it appear that some steps forward have been made, although they have been kept in a minority role.

2.3.3 The multiple aspects and problems of patient participation.

The principles of a more active and protagonist role of citizen-patients might appear rather obvious and coherent with the general trends of an increasingly 'liquid' society. Their

concrete application, however, in one of the areas of medicine has proven to be a rather complex and fragmented process.

While indeed the explicit criticism of the long-standing and substantially unchallenged paternalistic attitudes was easily acclaimed as an overdue step towards a more democratic relationship between doctors and their patients (148-152), the ways to translate the formal agreement into concrete different attitudes and actions became more a matter of studies than a straightforward implementation on a wide scale (153).

One of the most successful areas of analysis and experimentation has been that focusing on the definition and yield of 'shared decisions' in diagnostic therapeutic management (154-156). It is easy to see from the literature that the agreement on the importance and on the rights of citizen-patients, to an open partnership in assuming decisions has been of greater interest for social-psychological experts than for medical investigators and practitioners. The conditions required for implementing procedures of shared decisions appear to conflict with the routine condition of care, both in the hospital settings and in general practice. As well as the limitations, due to the shortage of the time needed to establish conditions of dialogue and reciprocal recognition, there is the deeper intrinsic difficulty of a change in the real hierarchy of power and knowledge that is reproduced in every encounter between those who are 'in charge', and have the competencies, and those who 'have the problems' (e.g. diseases, disability, needs) and are by definition not in the condition of equal cultural participation. Shared decisions are permanently at risk of becoming more a case of informed obedience to, or compliance with, what doctors' careers decide, than an interactive confrontation of points of view.

The 'informed consent' is the perfect model of a process of formalisation that is a surrogate for any substantial modification of a paradigm of dependence. A similar observation can be made on the very extensive literature that has focused on the need and the active promotion of participation in the management of chronic-complex medical conditions, and even more so in elderly patients (157-163). The (somehow) obvious recognition that an informed patient is more compliant (at least in the short-to-medium term) and possibly easier to control is hardly translatable, and even less monitored and assessed, in terms of increased autonomy in making decisions.

Patients (their identity as 'citizens' disappears as soon as the process of participation is centred-directed to targets such as diseases and their management) are informed individuals who are offered the opportunity of being conscious clients.

The implications of these findings to PV, which is the focus of our interest, are clear: patients can be more alert and reliable in reporting (if correctly and repeatedly stimulated) also their medical side-effects, or even their subjective discomfort, from the time they are included in study protocols and/or in experiments that run for definite periods of time. It is very hard to find data and results that document that patients have incorporated the concept and the concrete possibility of being subjects in a permanent dialogue and confrontation with the point of view of 'their' doctors (and even less so with the requests of the regulatory authorities!).

Participation cannot be productive in terms of innovating PV as long as it remains an instrument for one or the other aspect of the quality of care (including adverse drug reactions reporting), but which does not have as a primary goal the creation of people who are capable

of sharing not only well pre-defined knowledge, but also uncertainties, ignorance cultural, differences, lack of confidence, and 'subjective' perceptions.

2.3.4 The roles of qualitative methods and tools.

A citizen-patient-centred clinical practice can promote effective participation only if those who are 'educating' recognise that they need the competence and the point of view of those who are educated. The observations proposed by one of the promoters of a participatory culture of PV on the intrinsic difficulty of doctors to recognise their resistance and ignorance in communicating even the basic (essential for PV) distinction between risk and harm (164), provides a good summary of the points made so far.

A participatory attitude and practice of PV cannot exist as a separate component of medicine. To become credible for patients, doctors must be aware of their need for the sharing of their ignorance on how to deal with conditions of uncertainty. PV is in this sense a test of the practicability of medicine that is permanently challenged in its ability to monitor and understand the expressions of the interplay between clinical-objective background problems (symptoms, diseases) and the associated subjective effects-reactions that can be caused by the evolution of the (mis)management of the underlying disease.

An important area for the development of a culture and a practice of effective participation along these lines has been that of qualitative research where the contributions have been produced through a broad spectrum of methods and strategies that are briefly outlined in Table 2.5.

Table 2.5 - *Brief description of the main qualitative methods.*

Methods	Main objective
Qualitative methods (165)	Qualitative health research in general aims to answer "what", "how" or "why" questions about social aspects of health, illness and health care.
Interviews (166) Structured interviews Semi-structured In-depth interviews	These are conversations where the main purpose is to explore issues or topics in detail. Usually these involve a structured questionnaire, with fixed choices of answers. Semi-structured interviews are characterised by open-ended questions These are less structured, and can cover only one or two issues, but in great detail.
Focus groups (167)	Focus groups are a form of group interview that explicitly includes and uses the group interaction to generate data, to explore people's knowledge and experiences. They can be used to examine not only what people think, but how they think and why they think in that way.
Narrative methods (168-170)	Patients tell their stories to share experiences, emotions, problems, etc. A daily diary is an example of a narrative tool to collect information on the occurrence of events, and the severity of these events (e.g. drug related problems).

Their importance for 'patient-centred directed PV' can be summarised in a few critical points:

1. The focus of qualitative research aims to integrate the attention on what happens with the how and the whys, and the objective descriptors with the subjective perceptions, and the causal relationships with the dynamics of interactions. It is in this sense a potentially ideal approach-tool for addressing areas where the exploration of uncertainty occupies an important space.
2. Individuals with problems to be investigated are the protagonists, and their variability is the object of interest, not a confounding variable to be controlled for. Subjects are requested to speak in the plurality of their languages, without being obliged to comply with the rules of standard questionnaires, summaries or forms.

3. Personal histories are considered not only possible, but even privileged clues or guides to produce knowledge and innovative understanding of general problems (ideally, not to substitute, but to provide a complementary point of view) relating to classical side-effect reporting.
4. What is 'suspected-possible' because of the consistency of clusters of different pieces of evidence that however does not reach the statistical level of significant probability is not rejected as absence of informative power, but is considered as part of a process of approximation, and certainly as a significant description of one real aspect of reality. Subjectivity is recognised as one of the components of the objectivity of what all of us are, even if the patho-physiological background of the way perceptions, emotions and beliefs produce objective signs, symptoms and outcome events are certainly less known-understood.
5. The truly critical point of qualitative research parallels that of quantitative research: the difficulty (and most of the time the inability and unwillingness) of both sides of seeing each other as partial (and therefore important) points of view on issues-problems that are by definition multifaceted and cannot be fully understood nor appreciated by either single point of view.

2.3.5 The languages of citizen-patient-based pharmacovigilance must be many.

Possibly the main and comprehensive implication of the reflections, points of view and suggestions that have been made so far can be summarised as follows: as a branch of public health as well as a culture that should actively involve the daily perception of citizens, and not only of patients and specialists, PV can respond appropriately to its tor only if it can diversify

its contents, method and languages as requested by the variability and the specificity of the problems, populations and actors who are involved.

This last paragraph confirms the above statement by more directly introducing scenarios (not as a systematic overview, but synthetically via a few model cases) (Table VI) that document the need, the practicability, and the yield of such flexibility.

According to the mainly methodological objective of the whole chapter, it is certainly not necessary to describe the details of the experiences that are quoted. It should suffice to outline the framework, as based on Table 2.6, and to highlight their 'languages' as one of the most interesting contributions to PV.

Table 2.6 - *Brief descriptions of the model cases of citizen-patient participation in pharmacovigilance.*

1	"Power and Dependence - Social Audit on the safety of medicines" (171)	This book discusses the safety of medicines from a consumer perspective. The two main themes, power and dependence, are described in a detailed case-history of the prescribing of tranquillisers and sleeping pills over the past 200 years.
	"Medicines out of Control? – Antidepressants and the conspiracy of goodwill" (172)	This draws on the selective serotonin reuptake inhibitors (SSRIs) antidepressant case histories to describe a system of medicine control that was tainted by secrecy and conflicts of interest, and was barely accountable to the public. It also lacked common sense and lost sight of the meaning of health.
2	PARI FV Study (173,174)	This is a prospective study that was designed and realised by a network of Italian nurses who defined a PV project in a network of nursing homes. Among the 2214 patients who had 'problems', 519 drug-related problems were identified and described in detail, and analysed from the point of view of their 'avoidability' and of the specifically contextual determinants.
3	Caregivers as key actors in PV (65)	A prospective pilot study of the yield of two parallel monitoring programmes of side effects in psychiatric patients, which documents an up to 4-fold higher reporting of side effects by relatives than by the care doctors.
4	A successful BBC TV documentary programme as a vocal alternative to CSM (175)	Confronted with the prolonged official downplay of safety problems related to the most-prescribed SSRIs, the information given 'generated' over a week 1,374 emails that reported adverse events due to paroxetine.

5	Oxford-based health Dipex charity (176) (websites: Healthtalkonline and Youthhealthtalk)	Established in 2001 by Ann McPherson and Andrew Herxheimer after their own experiences of illness, Dipex aims to give direct voice to people living with a broad range of health conditions. Their clips reproduce in-depth interviews and are featured on their websites.

1. The first description in Table 2.6 is the books that tell the history of benzodiazepines and selective serotonin reuptake inhibitors (SSRIs), which were authored by one of the most important protagonists in the area of independent drug information directed for public opinion, who has also been working with great efficacy in the defence of citizens and patients rights in legal cases. They are hardly, if ever, quoted in the literature of PV, although they provide the clues to understand how and why two model categories of 'controversial' drugs (both from the point of view of efficacy and safety) became not only blockbuster products in the market, but a social phenomenon.

The 'linkage' proposed among the sources of information, and the competences that embrace pharmacology to sociology, to economics, to anthropology, to mass-media, to individual and collective psychology, produce a picture of the psychotropic drugs world that is far more telling on the determinants of the iatrogenic and dependence-producing potential of these drugs than any epidemiological or safety report of PV. The language is very precise, as in a book of history that can be read by everybody; it should be for problems (such as anxiety and depression) that belong to everybody, much before being a disease and/or a specialised area of medicine. It is interesting, on the other hand, to note that the penetration of the problems of this lay perception of the deeper meaning of PV in society found even broader and more popular expression in a best seller thriller (177). This insists on the basic mechanisms that are beyond the greatest issues of drug safety, those that are normally pushing

for the transformation of non-medical needs or problems in life into diseases, and therefore promising market areas, where the public-health profile and the role of drugs (see Table 2.6) are inevitably downplayed in favour of their propaganda.

2. Among the actors in PV, nurses are often quoted and recommended as a privileged point of observation because of their proximity to the patients and their specific competence for providing care, and not only in the diagnosis and treatment of clinical problems. Their PV reports are, however, very rarely quoted in the literature (and even less in documents for regulatory decisions), except when nurses act as 'transcribers' or 'secondary sources' of information for doctors. Something is moving, however, in the literature and in the legislation, although with an excess of restrictions and caveats. The second experience reported in Table 2.6 is mentioned not only because it is very close to the framework of action where our work has been generated, but because it focuses on a population (the elderly in nursing homes) that is certainly widely quoted in the literature as a major problem also for 'classical' PV, although mainly with a drug-centred approach: e.g. to document the well known (and obviously expected) proportional increase in side-effects with higher levels of exposure to 'drugs'. The approach was adopted by a network of nursing personnel who activated the research (including non-professional caregivers), and it is totally different. The focus is on the vigilance of all situations that document or raise a problem or a concern of non-autonomy, specific discomfort, confusion, or agitation (i.e. the most frequent problems for this population). The presence (or excess) or absence (e.g. due to non-availability) of pharmacological or non-pharmacological interventions are investigated as one of the possible determinants of the 'adverse events', of which those related to drugs are one expression. It is

possibly worth stressing that not only in Italy, for the populations and settings of nursing homes, the availability of medical personnel is often scarce for the monitoring of the situation. Furthermore, the language of official reporting of side effects and adverse reactions is largely inadequate for the description, ascertainment, and/or official recognition of the problems that characterise the lives (not simply the diseases) of these elderly citizens (who are also patients).

3. The third experience of Table 2.6 touches an even more neglected area, which was already briefly mentioned in Chapter 1: the role, culture, and language of the caregivers (family members or not) in the care of psychiatric patients who are mostly at home, and who only sporadically attend the health services. The impressive higher numbers of reports produced in this pilot study by these actors in their 'vigilance', compared with the parallel PV provided by doctors, is not only the reflection of the closer attention through the hours (nights and days) of real life. This indicates that for this population the expectations of observers (their cultural and conceptual framework, and therefore their language) determine the identification and the 'signals' of safety-acceptability problems. According to caring doctors, sedation is a 'desired' effect, and not an adverse effect of antipsychotics. It translations into a lack of autonomy, an 'absence' from daily activities, and such non-communication is considered as an event to be avoided-minimised only by those who care for the life of their loved ones, and not only for the burden of their disease.

4. The fourth experience (Panorama) has already become a classical case in the 'history' of PV, at least when this history is taken in the meaning highlighted in the comment of the first

scenario of Table 2.6. The substantial disregard of the population and individual safety problem of SSRIs has been challenged via a mass-media programme, where the language of 'information' was integrated with a formal invitation to take action, and to speak out. The results went above any expectations and forced the authorities to act. The knowledge produced was certainly not validated as a formal epidemiological report, where all events are cross-checked for their medical details (to be disregarded or rejected if they do not comply with all of the pre-defined criteria), but it was culturally (and profoundly; i.e. for the life of society and of its perception and awareness of the problem) far more informative and effective.

5. Dipex could be hardly considered from a formal point of view as a component of PV. As an expression of 'narrative medicine' in the language, and with the instruments of non-medical communication, it is however provocative documentation (and a powerful educational tool for the widest use) that interventions (with or without drugs) cannot be interpreted or qualified (in terms of efficacy, safety, and acceptability) if they are separated from the comprehensive perception and expression of the life and diseases of the subject.

CHAPTER 3

The cultural and methodological context of the research programme.

3.1 The general framework.

The years around the turn of the second millennium, when my pre-doctoral experimental training switched to a clinical pharmacy and epidemiology-oriented setting (which appeared to me more attractive and coherent with my basic interests), could be described at the national and international level as a scenario of contradictory, although at the same stimulating, evolution.

The most significant innovation of the last decade of the XX century in the area of the evaluation of health intervention (drug and non-drug based), was evidence-based medicine. This is a methodology that had also developed into a movement and a world-wide arena of collaboration, and it was facing three complementary challenges and open questions:

1. How to translate the efficient production of systematic knowledge into effective practices (from evidence-based medicine to evidence-based practice), with the participation of the different actors, from specialists to general practitioners, to public pharmacists, to nurses, and to patients;

2. What to do with the areas that appeared even more clearly with the systematic screening and assessment of the existing controlled randomised evidence, as 'grey', that were not investigated (e.g. those related to older age, to rare as well as complex clinical conditions, such as the control of symptoms, and to oncology);

3. Can the experience gained in the assessment of efficacy be used to focus on a more comprehensive view of the safety aspects, which should include the perception and satisfaction of the patients?

The setting of the Laboratory of Pharmacoepidemiology where I started working in 2001 could not be better, to allow me to be exposed from inside to the cultural and methodological problems linked to the challenges and questions briefly summarised above. The profile of the scientific activity of the groups working in the same Department was the best documentation of the richness and of the broadness of the opportunities and of the stimuli which were routinely available. From drug information strategies to the editing of the Italian Society of Hospital-Clinical Pharmacy (SIFO), which has its research center in the Consorzio Mario Negri Sud. From the advanced methodologies of pharmacoepidemiology, to the outcome research projects that also included qualitative and patient-based measures. From multicentre large-scale population trials, to the management and monitoring of networks dedicated to rare diseases. From hospital-based and general-practice-based investigations with a mix of pragmatic and very sophisticated design, to adapt to the different areas of interest; these included cardiovascular disease, diabetes, oncology, cognitive, behavioural and

psychiatric problems, and economic assessment, and came with the support of leading research units in the area of statistics and data management.

The early involvement in an international project as a representative for SIFO at the European level and a member of the Research Committee of the European Society of Clinical Pharmacy (ESCP) represented another enriching and provocative opportunity that allowed me to become more directly aware of the most promising trends in international scenarios.

3.2 Looking for a more focused approach.

Pharmacovigilance appeared to be an interesting area on which to concentrate my personal research activities for many reasons, including:

1. The explosion of highly controversial cases that documented the failure of the existing systems of monitoring of safety and appropriateness of the various phases in drug development and use (35, 36, 42, 46, 48);

2. The importance of patient involvement in the assessment of the benefit/ risk profile not only of specific drugs, but also of strategies of care;

3. The need for the creating of permanent networks of institutions and health professionals who were able to produce timely reliable data on controversial issues;

4. The opportunity of applying different research methodologies, with the complementary contributions of clinical pharmacology and epidemiology;

5. The opportunity of a close interaction with the different health actors and a spectrum of clinical disciplines;

6. The challenge of promoting research networks based on Departments of Clinical Pharmacy, to integrate the available competences, and of the diffusion of existing information on drugs and therapies, with the ability to produce original knowledge in 'orphan' areas of health care.

The research program for a research career was in this sense formulated as a coordinated effort that should include and be characterised in terms of:

- A systematic critical review of the most often fragmented experiences of regulatory-oriented and independent projects focused on safety aspects, to try to re-conceptualise PV as a comprehensive strategy that is aimed at including all aspects of the life of a drug in the community;

- The selection of topics of interest to be investigated with well targeted, and possibly integrated, field projects;

- The adoption of a spectrum of research methods that allow suitable approaches to clinical and epidemiological problems with different characteristics and therefore research needs.

3.3 The general operational plan.

The PhD programme was planned as a strictly individual activity, and I had to assure every technical aspect of the work, from the formulation of the general hypothesis to the working protocols, to data collection and quality control, and to the analysis of the data and the report writing. On the other hand, I had the support when needed of:

- the secretarial staff of the Study Centre of the SIFO, for all administrative and operational activities requested by the activation and implementation of external work with hospitals and general practitioner organisations and networks;
- the colleagues and resources dedicated to computing and statistical analysis;
- the regular discussions with my Director of Studies;
- the regulatory competence and support of the units in charge of interactions with ethical committees, to which, according to the national legislation, the protocols of observational outcomes studies collecting clinical data had to be submitted for general approval, with specific emphasis on the respect of privacy rules.

A particularly critical phase of the work that occupied an important part of the planned research schedule was devoted to the discussion and in-depth investigation of the opportunity of concentrating the focus of my research on qualitative indicators and instruments. This had

appeared to my second Supervisor, Professor Nicky Britten, as the most innovative and promising for patient-based PV. The development of the work on the overall re-conceptualisation of PV and the decision of Professor Nicky Britten to interrupt her intensive and intellectually very challenging tutorship, led in the end to a more balanced distribution of the theoretical and practical focuses of the research programme. Strictly qualitative instruments and investigational design could best provide useful new knowledge if they were part of more epidemiologically oriented field investigations. This served as a 'quality control' and provided a more in-depth view, with the capacity for quantitative data to adequately represent the benefit-risk profile of the index drugs/ therapeutic strategies, by the incorporation of the subjective perception of patients for the safety and satisfaction aspects of their drug experience, as well as of the problems arising from the interplay between patients and prescribers.

3.4 The organisation and the implementation of the field activities.

By definition, the detailed presentation, justification and discussion, of the methods, operational aspects and results of the various sub-projects that were developed for my PhD project are an integral part of the various projects and are described in the following Chapter.

As each characteristic required a specific research strategy, I report here only the essential characteristics of the approaches that were adopted and strictly adhered to specifically in the field projects.

Administrative databases.

The first phase of my research project consisted of an analysis of administrative databases to monitor new drugs in the real world among the general population; i.e. in a very large sample, to monitor specific potential adverse reactions.

The main research questions can be summarised accordoing to the following points:

1. Which would be the best methodologies and epidemiological criteria to identify and qualify sub-populations:

- with chronic 'index' clinical conditions, such as osteoarthritis?
- with co-morbidities?
- with different profiles of morbidity burden, and for this reason expected to be at higher clinical risk?

2. What are the patterns of drug exposure in the above sub-populations that identify:

- specifically drug-related risks?
- an increased burden of care (e.g. hospitalisation)?

3. Definition and testing of models for the analysis of the interplay of co-morbidities and poly-pharmacy in determining unfavourable clinical outcomes (e.g. adverse drug reactions; increased burden of care).

The linkage of administrative with demographics databases of the population included in the analysis allows the description of a comprehensive epidemiological profile of the case histories of the subpopulations of interest.

As well as the critical selection and use of the epidemiological and statistical methods and tools needed to analyse the large databases that were assembled from the participating LHA and represented a pilot study, a very important component of my work was spent in close collaboration with colleagues in the computing Laboratory. This was necessary for the development of the metafiles that allowed the efficient and full quality proven exploration and analysis of the enormous and highly dispersed quantity of heterogeneous information of the various databases.

The Coxib study was developed with a LHA (Savigliano) and represented a pilot phase to test and document the feasibility of monitoring risks related to new drugs through the linkage of Hospital Discharge Databases and Pharmaceutical Drug Prescription. Following the results obtained through the Coxib study, a specific *ad-hoc* project was carried out in the Piedmont Region in collaboration with Pharmacists of the LHA, to monitor a population with osteoarthritis through the linkage of health-care databases.

Epidemiological field work.

The following steps and activities were closely followed (with the obvious marginal adoption due to the specificity of the individual projects):

1. Personal elaboration of the draft protocol;

2. Collective discussion, with my Director of Studies and the relevant colleagues;

3. Establishment of a working group, checking out of the interest and willingness to participate of colleagues, nurses, general practitioners and patients to be involved in the field studies. For each project, a small advisory scientific committee was created, to allow closer interplay, with the adoption of the final protocol circulated to them and to the candidate centres/ individuals for their acceptance;

4. Submission of the protocol to the relevant Ethical Committees for approval;

5. De-centralised meetings with the investigators, to activate the data-collection phase;

6. Monitoring visits, strongly orientated more to updates and discussion of the problems investigated (to motivate and keep up the interest), than to bureacrotic controls.

7. More generally, the rules enforced in Italy for outcome-oriented observational studies were observed (which reflect the principles of Good Clinical Practice – International Conference Harmonisation [GCP-ICH], related to data travelling and monitoring, and privacy rights).

8. Meetings with the investigators for feed-back on the results at the end of the analysis.

9. Submission of draft manuscripts of the reports to participants, to comply fully with the general aims of the research projects. According to the basic principles of the Study Centre of SIFO, these included the permanent progressive formation of a critical mass of more conscious professionals via their involvement in the production of new knowledge (see Section 3.1, General Framework).

In all of the projects, the recognition of the research project in terms of 'credits' was sought, and was one of the conditions for voluntary participation of the hundreds of colleagues of various disciplines with no economic incentives.

It was certainly the experience of the degree of interest that I have had, despite and including all of the expected and unexpected difficulties and problems, that has guaranteed over the years the (many time renewed) effort (as well as the reward) of being truly 'travelling investigators' that has allowed me to become a reasonably good expert on the national health system and organisation.

Articles and award obtained during my PhD programme.

ScurtiV, Romero M, Tognoni G. A plea for a more epidemiological and patient-oriented pharmacovigilance. Eur J Clin Pharmacol 2012; 68(1):11-19.

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Scurti V, Paire M, Cagliero E, De Camillis P, Corrado D, D' Ettorre A, Romero M. L'uso dei database amministrativi per attuare un progetto di farmacosorveglianza: il modello dei Coxib. Giornale Italiano di Farmacia Clinica 2002; 16(3):133-137.

Scurti V, Fanizza C, per il Gruppo di Lavoro Piemonte. Modello di analisi di database amministrativi per identificare la cronicità: il caso dei FANS. Giornale Italiano di Farmacia Clinica 2005; 19(1):4-14

Scurti V, Font M, Anecchino C, Monte S, Fanizza C, Andretta M, Mirandola M, Pinato S, Romero M. Epidemiologia della cronicità: definizioni, metodologia, scenari modello. Giornale Italiano di Farmacia Clinica 2005; 19(2):102-109.

Gruppo di lavoro ETEO. Epidemiologia dei trattamenti dell'emesi in oncologia. Giornale Italiano di Farmacia Clinica 2005; 19(4):359-365.

Oral communications –International Conferences

Scurti V, Paire M, Cagliero E, De Camillis P, Romero M. The use of COXIBs in the elderly population with cardiovascular diseases. In: ESCP 4th Spring Conference on Clinical Pharmacy, Lisboa-Portugal May 14-17 2003, 92-9.

Scurti V, Sichetti D, Sasso E, Romero M. Management of delayed chemotherapy-induced nausea and vomiting (CINV) at home: what patients need. In: ESCP 34th European Symposium on Clinical Pharmacy, Amsterdam-The Netherlands 2005; Abs book Pepi 256: -10.

Scurti V, Fanizza C, Sichetti D, Romero M, Tognoni G. Gastrointestinal risks in patients exposed to NSAIDs In: ESCP 33rd European Symposium on Clinical Pharmacy, Prague-Czech Republic October 20-23, 2004, abs.n. Pepi 352, 89.

Scurti V, Sichetti D, Sasso E, Romero M. Evaluation of emesis management in oncological patientsIn: ESCP 33rd European Symposium on Clinical Pharmacy, Prague-Czech Republic October 20-23, 2004, abs. n. PT2 88, 107.

Scurti V, Sichetti D, Sasso E, Romero M for the ETEO working group. Prospective, multicentre, observational survey on antiemetic treatment in oncological patients. In: MASCC 17th International symposium 2005; Abs book 04-038: -421.

Awards

Best Oral Communication, 34th European Symposium on Clinical Pharmacy, Amsterdam-The Netherlands 2005

Scurti V, Sichetti D, Sasso E, Romero M. Management of delayed chemotherapy-induced nausea and vomiting (CINV) at home: what patients need. In; Abs book Pepi 256: -10.

Young Researcher Award AISD bn (Associazione Italiana per lo Studio deL Dolore), Firenze, 23-25 maggio 2010. 33° Congresso Nazionale dell'Associazione Italiana per lo Studio del Dolore (AISD) – Le nuove frontiere della medicina del dolore. Scurti V, Fanizza C, Sasso E, Romero M. La gestione del dolore nel paziente osteoartrosico in medicina generale: il progetto OMG.

CHAPTER 4

Results: Macro-analysis: population-based study through the analysis of administrative databases.

4.1 The use of administrative databases for a drug surveillance project: the Coxib model.

4.1.1 The general framework.

Coxib class of drugs occupied an important part of the first decade of the XXI century. There is no doubt that their history can be considered a comprehensive case model of all of the ambiguities that characterise the process of drug development, registration and surveillance. The details of this history have been so well documented in the literature that I could simply refer to a few of the key papers that highlight the roles of the various protagonists of the scenarios, from industry to the regulatory authorities, to the marketing strategies, and to the totally passive behaviour of the prescribers (178-180). For the purpose of this project, the safety of the Coxibs is specifically interesting in its rather early phase, which coincides with its marketing boom of the drugs. This was mainly based on their overall safety profile that was emphasized over and again as the major reason for preferring these newcomers to the old non-steroidal anti-inflammatory drugs (NSAIDs) (181, 182).

As soon as a (strong) suspicion of an important and unexpected risk (increase in cardiovascular morbidity and mortality) was raised by the meta-analysis of the published trials and findings of observational studies (183, 184), the hypothesis was formulated that it could be of great interest (both from the methodological point of view, and for public health implications) to explore whether and how the 'local' level of medical practice might be a suitable setting to test:

- the robustness of the suspicion;
- if ther was suspicion, its concentration in sub-populations at higher (pre-existing) risk of cardiovascular events;
- the timing of appearance of the causal association between exposure and events.

A very specific further reason for interest in the adopting of the scenario of th LHA area was the possibility of more directly involving a broad and heterogeneous group of prescribers in a study that was meant to show that routine data of the prescribing practice can be used for research purposes and can become tools for permanent education.

A methodological hypothesis to evaluate the epidemiological relevance of the problem.

The problems emerging from the international literature provided the grounds for a research project proposed by the Area Pharmaceutical Service of ASL 17 in Savigliano (CN, Piemonte), with the objective of observing and describing the populations treated with Coxibs through the use of administrative databases, i.e. the NHS list, the 2000 and 2001 prescriptions database, and the 2000 and 2001 hospital discharge database of the three hospitals in the area.

The study intended to assess the possibility of conducting a drug surveillance study through database linkage, and the monitoring of drug use and events that indicate a possible cardiovascular risk.

4.1.2 Methods.

The study involved the use of the administrative databases of a LHA (Savigliano-Piemonte) for the years 2000 and 2001, the NHS list, the prescription database, and the hospital discharge database.

Prior to record linkage, the databases were validated by checking the completion level of the data and by identifying duplicates. The data analysis was carried out using the SAS software system.

From the prescription database, all of thte prescriptions for Rofecoxib and Celecoxib (Coxibs; identified by the ATC code M01AH in 2000, and M01AH01 and M01AH02 in 2001) were selected and compared with the prescriptions of traditional NSAIDs (ATC code M01A from which Coxib ATC codes were excluded).

The linkage of the NHS list with the prescription database was carried out through the patient NHS number reported on each prescription, and this allowed the identification of the population exposed to those prescriptions. Only patients $\geq$45 years of age were included in the analysis, as these were the most exposed to chronic treatments with NSAIDs and at higher risk of cardiovascular events.

To assess the degree of exposure to Coxibs, the number of boxes prescribed to each patient during the period under study was calculated (July 2000-December 2001), and the population was divided into occasional users (1-2 boxes) and chronic users ($\geq$3 boxes). The

chronic users were further classified as low-exposure (3-5 boxes) and high exposure (≥6 boxes).

To define the specific subgroup with cardiovascular comorbidity (and therefore at higher risk of possible cardiovascular toxicity induced by Coxibs) within the population of occasional or chronic Coxib use, those patients also prescribed cardiovascular drugs (GAP: C) were identified and subdivided in terms of:

- Number of cardiovascular drug prescriptions;
- Time of exposure with respect to Coxib consumption (6 months before and/or 6 months after).

In the final part of the analysis, the record linkage with the hospital discharge database of patients exposed to Coxibs allowed the identification those who underwent hospitalisation for cardiovascular causes (ICD-9CM: from 401 to 414; 426 to 440; 451), both within the 6 months preceding and within the 6 months following the Coxib prescribing. The number of hospitalisations was also determined for patients prescribed cardiovascular drugs. Figure 4.1 shows the main steps in the analysis. From the general population of the Savigliano LHA, the subjects ≥45 who received these drug prescriptions were identified, and among these, those treated at least once with Coxibs. Within this population, the patients prescribed both Coxibs and cardiovascular drugs were identified. The two populations (Coxibs only, and Coxibs+cardiovascular drugs) were then stratified according to age and subdivided with respect to number of boxes prescribed. Finally, record linkage with hospital discharges within these populations identified those with hospitalisation for cardiovascular causes in the period preceding or following the beginning of the Coxib prescribing.

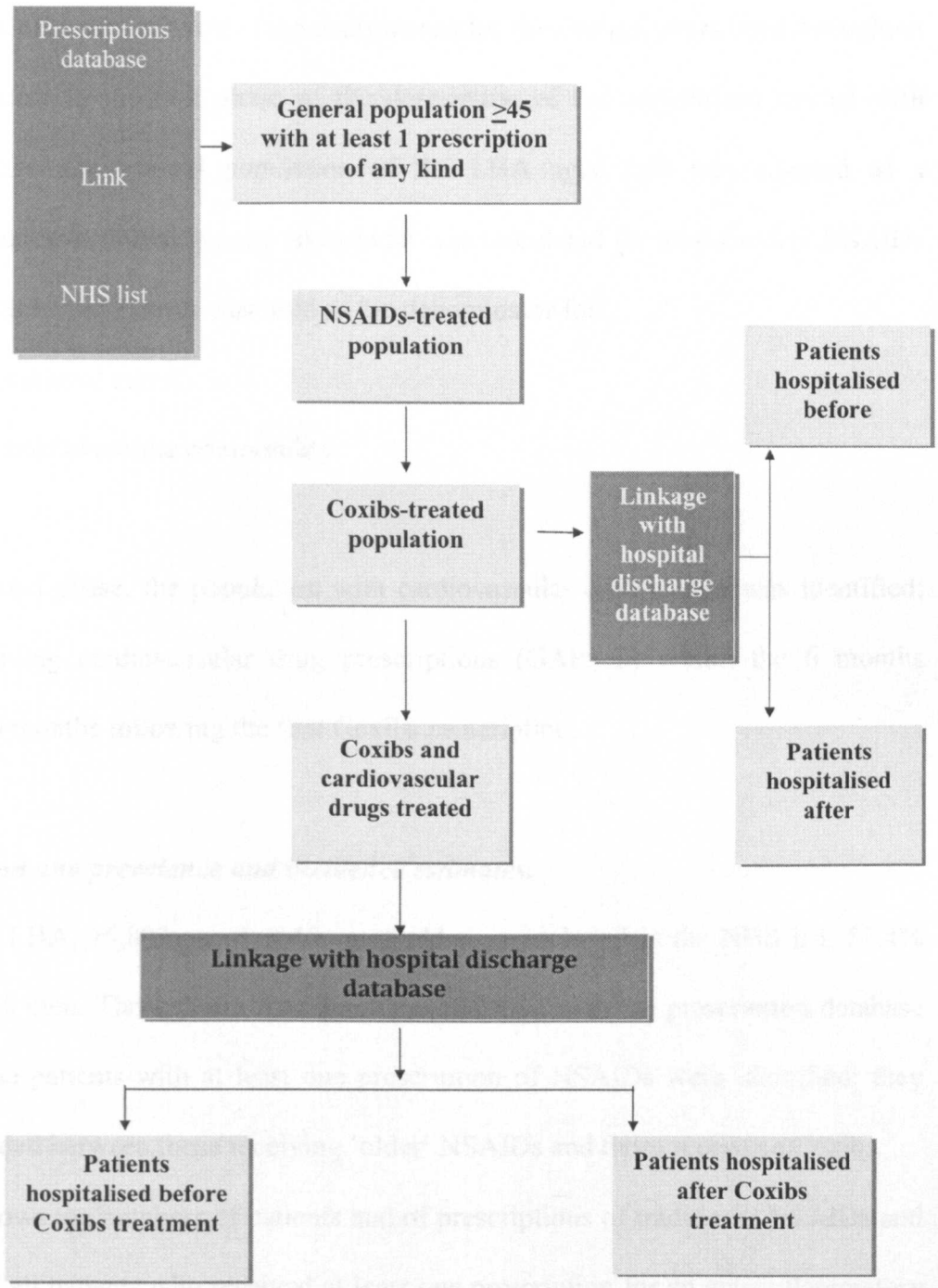

Figure 4.1: *Algorithm for identification of the study sample.*

4.1.3 Results.

Before starting with the presentation of the analysis results, the denominators used throughout need to be specified. In the first phase of the description of the populations treated with Coxibs or NSAIDs, the general population of the LHA aged ≥45 was adopted as a denominator. Patient distribution by age and gender was calculated for total Coxibs/ NSAIDs users. The group receiving Coxibs was used as the denominator for:

- Chronic or occasional users;
- Patients with cardiovascular comorbidity.

In the second phase, the population with cardiovascular comorbidity was identified; i.e. patients receiving cardiovascular drug prescriptions (GAP: C) within the 6 months preceding or the 6 months following the first Coxibs prescription.

General population and prevalence and incidence estimates.

In the Savigliano LHA, 75,893 people ≥45 years old were included in the NHS list, 52.4% women and 47.6% men. Through the linkage of the NHS list with the prescription database for 2000-2001, the patients with at least one prescription of NSAIDs were identified; they were then subdivided between those receiving 'older' NSAIDs and those receiving Coxibs.

Table I shows the numbers of patients and of prescriptions of traditional NSAIDs and Coxibs: 25.2% of all patients who received at least one prescription for an anti-inflammatory drug over the period under study were treated with Coxibs (5,503/21,823).

With respect to the entire LHA population, 7.2% of the people ≥45 years old received at least one Coxib prescription, and 21.5% at least one NSAID prescription, during the period

under study, and therefore the *prevalence* of Coxibs use was 72.5‰ inhabitants ≥45 years old, and 215.0‰ for NSAIDs. The *incidence* was calculated by identifying the new anti-inflammatory drug users (i.e. those who had not received any anti-inflammatory drugs over the 6 months preceding their first Coxibs or NSAID prescription), which was 45.6‰ for Coxibs use, compared to 139.5‰ for NSAIDs.

Table 4.1 - *NSAIDs use, July 2000-December 2001.*

	Patients		Prescriptions	
	N.	%	N.	%
Traditional NSAIDs	16320	74.8	38940	75.8
Coxibs	5503	25.2	12431	24.2
Total	**21823**	**100**	**51371**	**100**

The population age-specific incidence of Coxibs and traditional NSAID users is reported in Figure 4.2. Overall, NSAID use increases over 65 years of age; those most exposed to both Coxibs and NSAIDs were between 75 and 84 years of age.

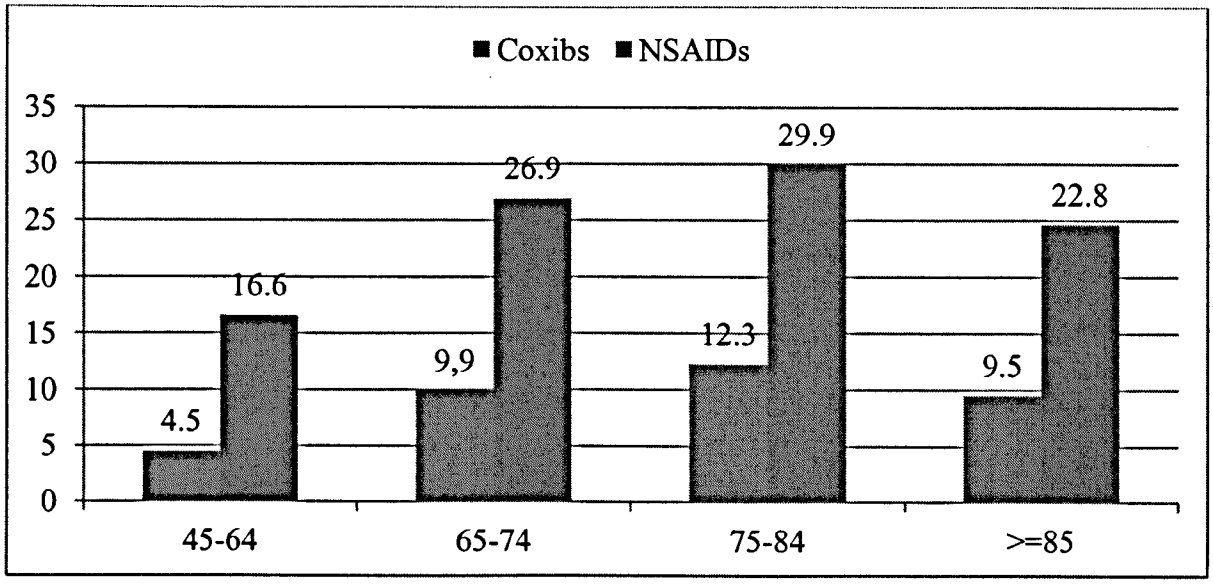

Figure 4.2: *Population age-specific incidence of Coxibs and NSAIDs users.*

Coxibs/NSAIDs users.

Table 4.2 shows the age and sex distributions of the patients using Coxibs or traditional NSAIDs: 65.6% of Coxibs users and 57.5% of traditional NSAID users were ≥65. Women represented 69.3% and 61.8% of those receiving prescriptions for Coxibs and traditional NSAIDs, respectively.

Both of these subgroups of patients were classified as occasional or chronic users on the basis of the number of boxes received during the period under study. Chronic patients were subsequently classified in terms of their degree of Coxibs exposure; 1,000 (55.1%) were defined as low exposure (3-5 boxes) and 803 (44.5%) as high exposure (≥6 boxes). Among the high exposure subjects, 73.6% were ≥65 years of age, while among the low exposure, this proportion was 69.9%.

Table 4.2 - *Age and sex distribution of patients receiving at least one prescription of Coxibs or traditional NSAIDs.*

Age	Sex				Total	
	Females		Males			
	No.	%	No.	%	No.	%
Coxibs users						
45-64	1259	22.9	636	11.6	1895	34.4
65-74	1187	21.6	597	10.8	1784	32.4
75-84	1002	18.2	355	6.4	1357	24,7
>=85	366	6.6	101	1.8	467	8.5
Subtotal	***3814***	***69.3***	***1689***	***30.7***	***5503***	***100***
Traditional NSAIDs users						
45-64	4009	24.6	2930	17.9	6939	42.5
65-74	2961	18.1	1916	11.7	4877	29.9
75-84	2226	13.6	1068	6.5	3294	20.2
>=85	883	5.4	327	2.0	1210	7.4
Subtotal	***10079***	***61.8***	***6241***	***38.2***	***16320***	***100***
Total	**13893**	**63.7**	**7930**	**36.3**	**21823**	**100**

Table 4.3 - *Occasional and chronic users.*

Age	Occasional users		Chronic users	
	No.	%	No.	%
Coxibs				
≥ 65	2318	62.7	1290	71.6
< 65	1382	37.3	513	28.4
Total	***3700***	***100***	***1803***	***100***
Traditional NSAIDs				
≥ 65	5660	54.0	3721	63.7
< 65	4817	46.0	2122	36.3
Total	**10477**	**100**	**5843**	**100**

Populations receiving Coxibs and cardiovascular drugs.

Three groups of subjects who were exposed to Coxibs were identified:

- Patients with a pre-existing cardiovascular comorbidity, i.e. those exposed to cardiovascular drugs in the 6 months preceding their first Coxibs prescription (Group 1);
- Those who were prescribed cardiovascular drugs only during the 6 months following their first Coxibs prescription (Group 2);
- Those who were exposed to cardiovascular drugs both 6 months before and 6 months after their first Coxibs prescription (Group 3).

Figure 4.3 shows these three groups stratified according to age. The patients who were prescribed cardiovascular drugs only after their first Coxibs prescription (Group 2) were younger than those in the other two groups.

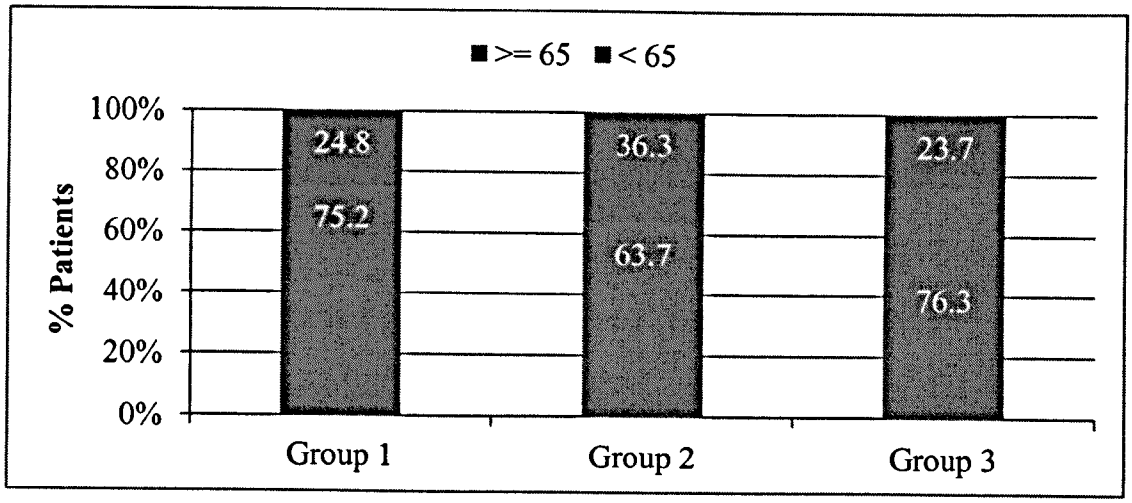

Figure 4.3: *Patient distribution by age classes and history of cardiovascular comorbidity.*

Exposure to Coxibs was then evaluated among the three groups to define the treatment continuity. The following Tables show the distributions of the occasional and chronic Coxibs

users within these three groups of patients (Table 4.4), and the degree of exposure among the chronic Coxibs users (Table 4.5). Although the differences within the subgroups are small, there is an excess of chronic Coxibs users in Group 2, as compared to the other groups (39.3% *vs* 34.5% in Group 1, and 36.1% in Group 3) (Table 4.4). Furthermore, the Group 2 patients appeared to be more exposed to Coxibs compared to the other groups: 50.4% (65/129) of the Group 2 patients were highly exposed, compared to 43.9% (511/1164) in Group 1 and 42.9% (469/1092) in Group 3. With respect to age, the patients in Group 2 were younger, regardless of exposure: 39.1% and 21.5% were <65.

Population assuming Coxibs and hospital admissions.

The analysis of the hospital discharge database indicated that among the LHA population >45 years old, 2,228 subjects were hospitalised for cardiovascular causes between July 2000 and December 2001; 83% of these were >64 years old. Hospitalisations for cardiovascular causes of patients receiving at least one Coxibs prescription were identified by linking admissions taking place in the 6 months preceding and the 6 months following their first Coxibs prescription. Overall, 64 Coxibs patients were admitted for cardiovascular causes in the 6 months preceding their first prescription, and 104 in the 6 months following. Among Group 1 patients, 63 were hospitalised in the 6 months preceding their first Coxibs prescription, and 92 in the 6 months following. In Group 2, no patients were admitted prior to heir first Coxibs prescription, while 10 were hospitalised in the following 6 months.

Table 4.4 *Occasional vs chronic Coxibs use by age.*

AGE	Coxibs			
	Occasional use		Chronic use	
	N.	%	N.	%
Group 1 (3372)				
≥ 65	1625	73.6	910	78.2
< 65	583	26.4	254	21.8
Total	**2208**	**100**	**1164**	**100**
Group 2 (328)				
≥ 65	119	59.8	90	69.8
< 65	80	40.2	39	30.2
Total	**199**	**100**	**129**	**100**
Group 3 (3032)				
≥ 65	1451	74.8	861	78.8
< 65	489	25.2	231	21.2
Total	**1940**	**100**	**1092**	**100**

For Group 3, 62 patients were hospitalised in the 6 months preceding Coxibs prescription, and 90 in the 6 months following. As shown in Figure 4.4, there were increases in the proportion of hospitalisations for cardiovascular causes within all three groups following their first Coxibs prescription; the increment was particularly evident for Group 2 (i.e. patients receiving cardiovascular drugs only within the 6 months following Coxibs treatment). These patients were also significantly younger, insofar as only 50% were ≥65 compared with 89% of all Coxibs users, 93.5% of Group 1, and 93% of Group 3. In addition, 11 of the patients hospitalised in the 6 months preceding first Coxibs prescription were hospitalised again in the following 6 months.

Table 4.5 - *Age and Coxibs exposure level among chronic Coxibs users in the three groups.*

AGE	Chronic Coxibs users			
	Low exposure		High exposure	
	No.	%	No.	%
Group 1 (1164)				
≥ 65	497	76.1	413	80.8
< 65	156	23.9	98	19.2
Total	**653**	**100**	**511**	**100**
Group 2 (129)				
≥ 65	39	60.9	51	78.5
< 65	25	39.1	14	21.5
Total	**64**	**100**	**65**	**100**
Group 3 (1092)				
≥ 65	476	76.4	385	82.1
< 65	147	23.6	84	17.9
Total	**623**	**100**	**469**	**100**

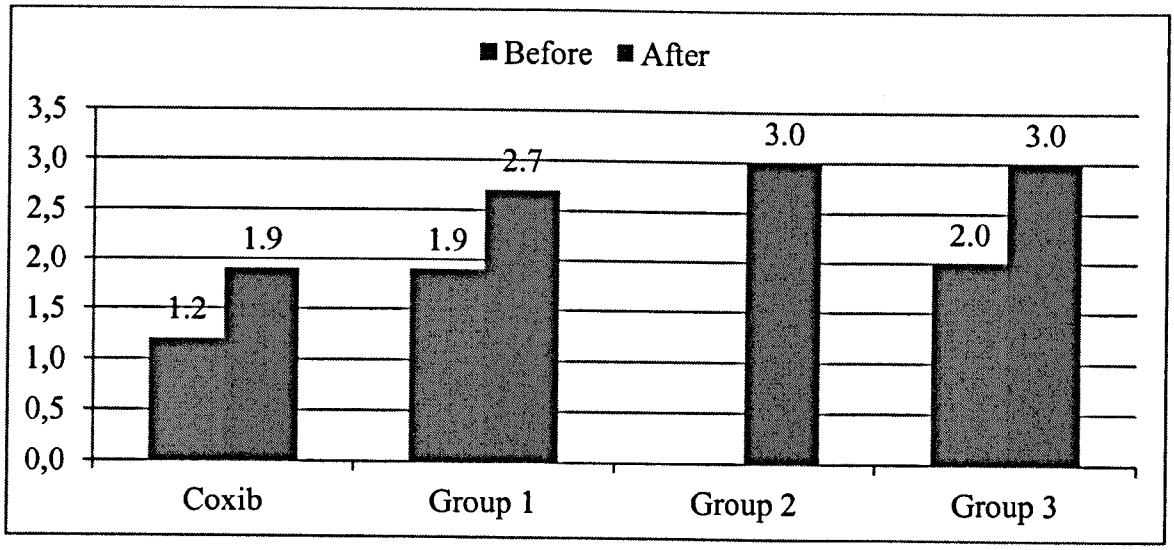

Figure 4.4: *Percentages of hospitalisations in the 6 months preceding and in the 6 months following first Coxibs prescription.*

4.1.4 Discussion and conclusions.

The aim of this study was to assess the feasibility and evaluate the results from an integrated use of administrative databases in a drug surveillance perspective, though the linkage of prescriptions and hospitalisations within a specific population.

The most important information obtained with this analysis can be summarised in two main points:

a) Data available from the records can be used for analysis of cohorts of patients also in a longitudinal design;

b) The great numbers of patients that can be identified and followed with these archives represent a very important resource, and also allow the identification of key events.

The linkage of the administrative data allows the monitoring in real time of eventual adverse reactions of drugs, especially during the first period after introduction on the market, when the drugs start to be used in large populations, rather than being selected as patients treated during clinical trials.

4.2 Administrative database analysis to identify chronicity: the case of NSAIDs and ostheoarthritis.

4.2.1 Introduction.

According to the American College of Rheumatology (ACR), osteoarthritis includes a heterogeneous group of joint conditions that result in a loss of integrity of the cartilage, and changes in the bone matrix and in the articular margins, with progressive loss of functional autonomy and increasing disability (185).

The main symptom of osteoarthritis is the pain elicited by the movement of the joint, which generally decreases when the joint is at rest. In advanced stages, there can also be nocturnal pain tha interferes with the sleep of the patient (186). In some cases, osteoarthritis is associated with joint inflammation and stiffness (particularly in the morning or during movements). Crackling (a sound due to the loss of cartilage and to the irregularity of the bone surface) and swelling (due to secondary synovitis or to proliferative changes of cartilage or bone, i.e. osteophytes) are further typical clinical signs. In the most advanced stages of the disease, there can be a complete loss of function, and in some cases deformity and formation of bone cysts (186,187).

The pharmacological approach to the symptoms of inflammation and pain is still one of the most controversial areas, because of the variability in intensity, duration, recurrence and achievable degree of symptom control. These results in the high variability of the therapeutic schemes applied in clinical practice, the efficacies of which are not always very

high, and which sometimes entail clinically relevant toxicity profiles or low tolerability (188-190).

The NSAIDs are widely used in the symptomatic treatment of pain and inflammation in osteoarthritis. However, their toxicity profile beyond the well-known risk of gastric damage still needs to be fully evaluated (i.e., cardiovascular toxicity), and their use requires constant monitoring, particularly since the majority of exposed patients are elderly, and, by definition, at higher risk (191). As has already been documented (192-198), the analysis of the administrative databases allows the identification of large cohorts of patients who would not be obtained through large clinical trials or through observational *ad-hoc* studies.

The possibility of observing and monitoring epidemiologically and clinically representative cohorts provides a very important resource, particularly for the study of chronic diseases, in so far as it allows clinical and care aspects to be linked together, to evaluate the course of clinical practice and to detect possible risk situations. This approach is very valuable in the study of osteoarthritis, a chronic disease with variable symptoms that are typical of the elderly, a population that is already characterised by many chronic diseases requiring continuous, long-term, exposure to drugs. The project, the protocol of which is summarised in the Appendix 1 (section 4.2.5), used administrative databases with the main objective of identifying the populations of patients with osteoarthritis through NSAID prescriptions, and thus to describe their therapeutic and clinical courses. The analysis model developed starts from the drug prescriptions, to identify patients with osteoarthritis, whose records are then linked to hospital admissions (due to the underlying disease or to other causes), to define subgroups of patients at higher risk or with higher disease severity. In this analysis, the definition of chronicity (of treatments and diseases) is extremely important.

Several approaches have been suggested, such as defined daily doses, the number of boxes/time, and the duration of the treatment (197,198). This analysis was specifically aimed at this point, and it illustrates the analytical model that is intended to identify the chronic conditions adopted by the study protocol, as a methodological contribution to the use of administrative databases in the study of chronic conditions.

4.2.2 Objectives.

This study was designed to test and validate a model of analysis of administrative databases in order to:

1) identify patients with osteoarthritis from the prescriptions of tracer drugs;
2) define chronicity by combining exposure levels and durations of treatment;
3) describe from an epidemiological and a clinical point of view the populations identified as above.

Strategy of analysis.

Through the analysis of the administrative databases of three LHA (patient register, prescriptions, and hospital discharge databases), a cohort of patients with osteoarthritis was identified. From the prescription database and the patient register, the subjects exposed to the "tracer" drugs for osteoarthritis (i.e. NSAIDs, ATC class M01A) were identified. The linkage with the hospital discharges allowed the identification of the more severe or more complicated conditions, i.e. those requiring hospitalisation. The analysis was carried out over a 12-month period.

The population identified as above was examined both in terms of their exposure level to the tracer drugs and of their treatment duration. As previously noted, osteoarthritis is a chronic condition with extremely variable symptoms and therefore variable treatments, that is closely dependent on the general conditions of the patients. Therefore NSAIDs can be used more or less continuously or over short periods of time and periodically repeated. The first aim of the analysis was therefore that of identifying chronicity within the population of NSAID users, following 'classic' and 'integrated' methods.

The classic method, as previously reported (Section 4.1, and 196, 197), uses the number of boxes that each patient was prescribed over a given period of time. In this case, the patients are defined as 'occasional users' if they received a prescription of up to two boxes of NSAIDs over a 12 month-period, and 'chronic users' with three or more boxes. If there is a high variability in the number of boxes prescribed, the latter group is usually divided into (generally two) subgroups: patients with 3-5 and patients with 6 or more boxes. This strategy allows the identification of subgroups of patients with occasional or continuous exposure to the treatments, but does not allow the qualification of the size or the duration of their exposure, and provides therefore a somewhat 'static' picture of the problem.

The integrated approach, on the other hand, combines the number of boxes (and/or prescriptions) with the duration of treatment, which allows better evaluation of the size of exposure as well as the identification of patient subgroups with different pain severities. This provides a more 'dynamic' (and more realistic) perspective to the problem. This analytical strategy was developed in three steps:

- The first sep identifies the number of prescriptions (not of boxes) issued over a given period of time (i.e. a year) and defines the exposure level: one prescription indicates low exposure, two, intermediate exposure, three or more, high exposure;
- In the second step, the patients are divided on the basis of the length of time elapsed between the first and the last prescription (within the same time frame), thereby defining both the actual duration of treatment and the prescription frequency;
- The third step joins the two variables (number of prescriptions and time period) with the number of boxes prescribed, therefore calculating an exposure duration that is 'weighted' according to the number of boxes as a more direct indicator of treatment intensity.

Another variable taken into account was the age of the patients (a crucial component in the definition and evaluation of chronicity), to obtain more precise prevalence estimates (in the specific case of osteoarthritis, for instance, it is well known that it concerns the elderly population particularly), and to carry out a more pertinent analysis on the pharmacological treatments insofar as they can also represent (particularly among the elderly) a further risk factor.

Finally, the prescription database was linked to the hospital discharge database to identify the most severe or less controlled conditions, for which a hospital admission was required. Hospital admissions for osteoarthritis were specifically examined, and particularly the diagnostic groups of osteoarthritis and allied disorders, and other and unspecified arthropathies (ICD-CM: 715 e 716). The analyses were carried out using the SAS software, version 8.

4.2.3 Results.

Reference population and NSAID-treated population.

The population examined included 629,169 registered subjects, 323,724 (51.4%) women and 154,277 (24.5%) over 64 years of age. The subjects with at least one pharmacological prescription were 421,417 (67%), of which 126,198, i.e. 20% of the general population, received at least one NSAID prescription. On average, the patients treated received 11 prescriptions of any drug. With respect to the subgroup of patients exposed to NSAIDs, on average each patient received 2.4 prescriptions of these drugs (Table 4.6).

Table 4.6 - *Reference denominators.*

Denominators	N°/%
Registered population	629169
Total treated	421417
Treated with NSAIDs	126198
% NSAIDs on total	29.9%
Total prescriptions (all drugs)	4634420
NSAIDs prescriptions	302450
% NSAIDs on total	6.5%
Total boxes (all drugs)	8083072
NSAIDs boxes	398688
% NSAIDs on total	4.9%
Average No. prescriptions/total treated	11
Average No. NSAIDs prescriptions/total treated	2.4

Women appeared to be exposed to NSAIDs treatment more often: 59.9% (75,562/126,189) of subjects who received NSAIDs were females. Prevalence estimates support this finding, since 24% of the women were exposed to NSAIDs versus 16.5% of the

men. The percentage of women exposed to NSAIDs is always higher than that of men also within age categories (Figure 4.5). Figure 4.5 also shows that NSAID use increases with increasing age, and that subjects 65-74 years old are more exposed, while at 85 and over the use of NSAIDs appears to taper off.

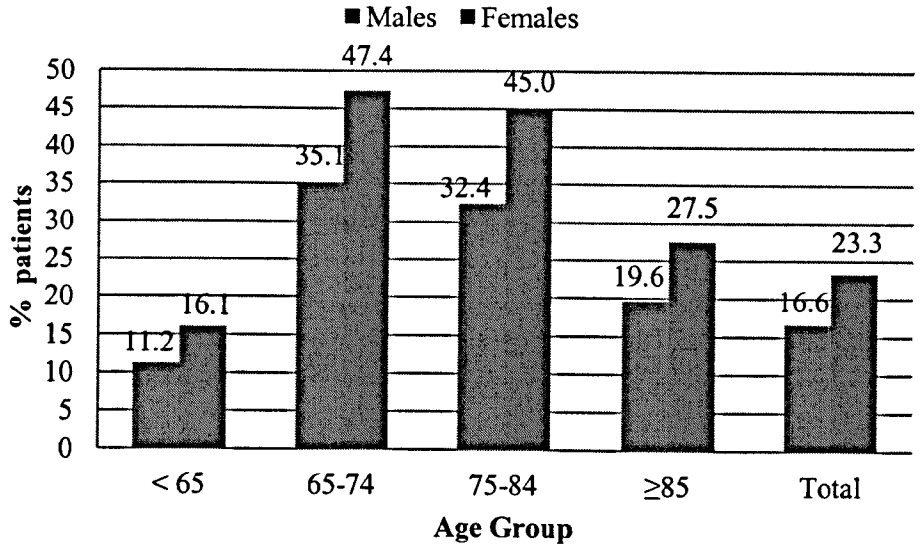

Figure 4.5: *Prevalence of NSAIDs use in the general population, stratified by gender and age.*

Chronicity evaluation.

The analysis of NSAID exposure according to the number of boxes issued identified two subgroups of patients defined, according to the criteria adopted, as occasional users (1-2 boxes/year) and chronic users (≥ 3 boxes/year). Among the 46,172 subjects exposed to NSAIDs, 36% were chronically treated patients, over 60% of whom receive between 3 and 5 boxes a year (Table 4.7).

If exposure is evaluated according to the 'integrated methodology' (see 4.2.2 *Strategy Analysis*), which considers the number of prescriptions rather than the number of boxes received during the year, the population can be subdivided in three groups: low (1 prescription/year), intermediate (2 prescriptions/year) and high (≥3 prescriptions/year) Exposure. The patients with 3 or more prescriptions/year numbered 35,953, as 28.5% of all of the patients treated with NSAIDs (Table 4.8).

Table 4.7 - *Distribution of the patients by type of exposure to NSAIDs.*

Exposure	No. Pts	%
Occasional (1-2 boxes/year)	***80026***	***63.4***
Chronic	***46172***	***36.6***
3-5 boxes/year	28223	61.1*
>= 6 boxes	17949	38.9*
Total	**126.198**	**100.0**

* % calculated on the total of chronically-exposed patients.

Table 4.8 - *Distribution of the patients by level of exposure to NSAIDs.*

Exposure level	No. Pts	%
Low	64412	51.0
Intermediate	25833	20.5
High	35953	28.5
Total	**126198**	**100.0**

The comparative analysis of the subgroups of patients identified through the two methods shows that the proportion of low exposure patients is lower than the proportion of occasionally treated patients (51.0% *vs* 63.4%). Similarly, the population at high exposure is smaller than that defined as being chronically treated (28.5% *vs* 36.6%). This indicates the presence among both occasional and chronic users of patients with an intermediate or variable exposure, an observation which would be related to the discontinuous course of the disease and the variability of the symptoms, and therefore of their specific treatments. The situation is even more obvious when the level of exposure is related to the treatment duration: while low-exposure patients received short-term treatments (1 month), and high-exposure patients basically received long-term treatments (≥6 months), the intermediate-exposure group showed a greater degree of fluctuation, including patients for whom treatment is limited in time, and patients with repeated treatments (Figure 4.6).

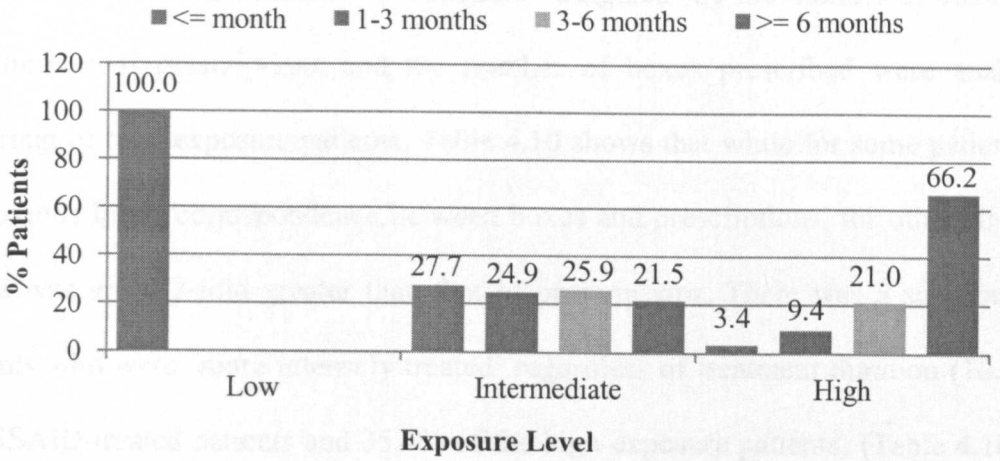

Figure 4.6: *Distribution of patients by exposure level and treatment duration.*

Among the 25,833 patients with intermediate exposure, 7,169 (27.7%) received both prescriptions within a month, while among the remaining 18,664, the interval varied between a minimum of 31 to a maximum of 363 days. For 5,536 patients (21.4%), the interval between prescriptions was over 6 months. High-exposure patients were mostly (87.2%; 31,350 patients) treated for over 3 months, and 66.1% (23,776 patients) was treated for 6 months or more (Figure 4.6). Among the 35,953 high-exposure patients, we sought to identify the subgroups undergoing intense (>4 prescriptions/year) and prolonged (>3 months) treatments. The data presented in Table 4.9 show that 21,644 patients (highlighted in the Table) were 'continuously and intensely' treated (representing 17.2% of the whole population treated with NSAIDs, and 60.2% of the high-exposure population). On the other hand, 1,210 patients (1% of those treated with NSAIDs, and 3.4% of those highly exposed) were intensely treated for short periods of time (patients receiving a minimum of 3 up to over 6 prescriptions within a month).

To evaluate the duration of exposure 'weighted' by the number of boxes prescribed, the number of prescriptions and the number of boxes prescribed were analysed in the subgroup of high-exposure patients. Table 4.10 shows that while for some patients there was an obvious linear correspondence between boxes and prescriptions, for others the number of boxes was up to 3-fold greater than that of prescriptions. There was a subgroup of 12,862 patients who were 'more intensely treated' regardless of treatment duration (10.1% of all of the NSAID-treated patients and 35.4% of the high-exposure patients) (Table 4.10). A further indication of the variable severity of osteoarthritis (or the changeable requirement of NSAID treatment) is provided by the frequency with which high-exposure patients saw their physicians, as shown by the intervals between the prescriptions.

Table 4.9 - *Number of prescriptions and treatment duration among the high-exposure patients.*

No. of prescriptions	Duration of treatment								Total	
	≤ 1 month		1-3 months		3-6 months		> 6 months			
	No.	%	No.	%	No.	%	No.	%	No.	%
3	946	2.6	2212	6.1	3886	10.8	5817	16.2	12862	35.8
4-5	249	0.7	1016	2.8	2830	7.9	8378	23.3	12473	34.7
≥ 6	15	0.0	167	0.5	855	2.4	9581	26.7	10618	29.5
Total	**1210**	**3.4**	**3395**	**9.4**	**7574**	**21.0**	**23776**	**66.2**	**35953**	**100.0**

Table 4.10 - *Distribution of high-exposure patients by number of boxes and number of prescriptions.*

No. of boxes	No. of prescriptions						Total	
	3		4-5		≥ 6			
	No.	%	No.	%	No.	%	No.	%
3	6199	17.2	-	-	-	-	**6199**	**17.2**
4-5	5434	15.1	6384	17.8	-	-	**11818**	**32.9**
≥ 6	1229	3.4	6084	16.9	10618	29.6	**17936**	**49.9**
Total	**12862**	**35.8**	**12473**	**34.7**	**10618**	**29.6**	**35953**	**100.0**

Table 4.11 shows that almost half of the patients (47%, 16,940/35,953) went to their doctor every 30/60 days. According to the numbers of prescriptions received, they appeared to be treated for a minimum of 3 to a maximum of 12 months.

On the other hand, the situation of 53% of the patients appeared to vary widely: 3,742 patients (10%) were treated continuously and intensively (≥6 prescriptions received at a maximum intervals of 30 days), while 1,967 subjects (5.5%) were exposed to long-term treatment (3/6 months) but with long intervals (90/120 days). Moreover, 1,412 (4%) patients were treated intensely for short periods of time (3 prescriptions within a month and a half at most) (Table 4.11).

Table 4.11 – *Distribution of high-exposure patients by number of prescriptions and mean time between prescriptions.*

Mean time (days)	No. of prescriptions			Total
	3	4-5	≥6	
<14	1412	734	434	**2580**
15-29	1649	1436	3308	**6393**
30-59	3777	6291	6872	**16940**
60-89	4052	4008	4	**8064**
90-119	1967	4	0	**1971**
120-179	5	0	0	**5**
≥180	0	0	0	**0**
Total	**12862**	**12473**	**10618**	**35953**

Chronicity, age of patients and therapeutic approach.

The use of NSAIDs increases with increasing age. Among the elderly (>65 years old), about 3-fold more patients receive NSAID treatment as compared with adults, i.e. 38.7% (59,733/ 154,277) and 14% (66,465/474,892), respectively. This increase among elderly subjects is also associated with an increase in the treatment chronicity and a higher exposure level. The

distribution by age of people treated with NSAIDs shows that the elderly (≥65) are most exposed and also more frequently treated continuously. In terms of boxes prescribed, overall, the elderly population represented 38.6% of those treated occasionally and 62.3% of those treated chronically. Within the age groups, the proportion of chronic patients among the elderly was over 50% also in the higher age groups (>85 years old) (Figure 4.7).

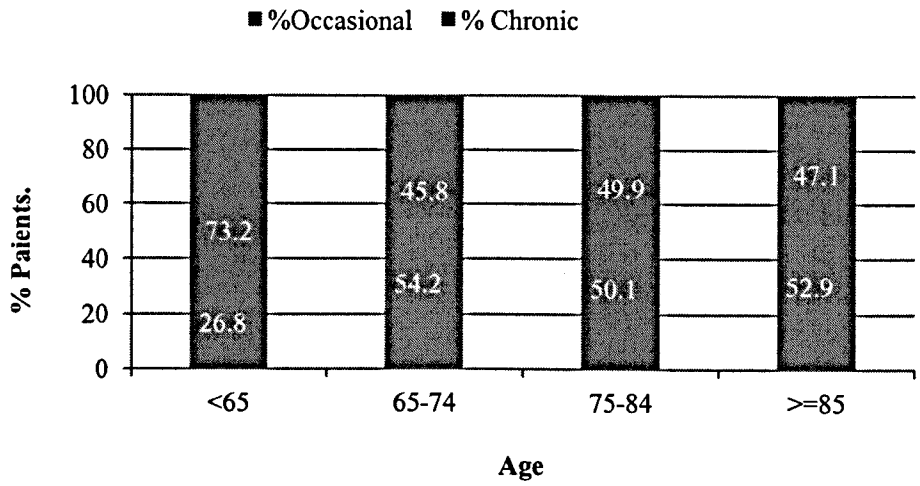

Figure 4.7: *Distribution of patients by age and type of exposure.*

The integrated methodology confirms this observation, showing that among the elderly, the number of patients highly exposed to NSAIDs increased and that of low exposure decreased, while the group with intermediate exposure did not appear to change throughout the age groups (Figure 4.8). As for the therapeutic approach (monotherapy *versus* polytherapy), chronic patients appeared to be exposed more often to polytherapy (72.2% vs 10.6% among occasional users), as well as highly exposed subjects (77% vs 54.9% among those with intermediate exposure).

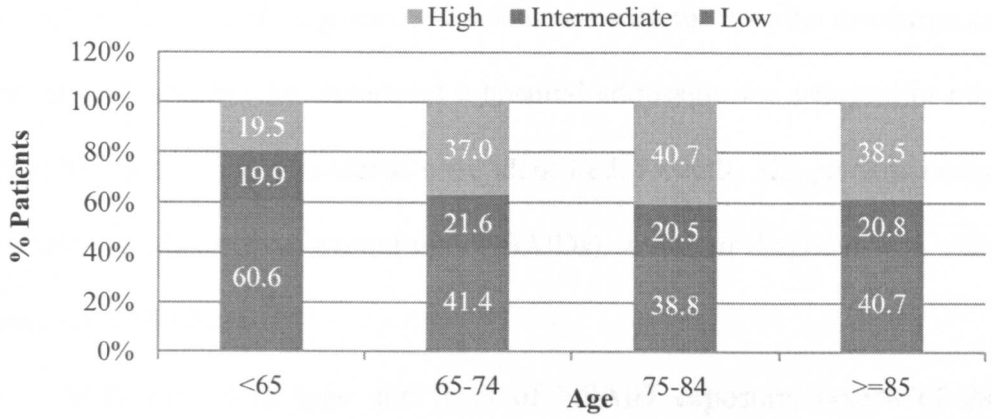

Figure 4.8: *Distribution of patients by age and levels of exposure to NSAIDs.*

With respect to exposure level, these results confirm once more that intermediate exposure subjects are atypical, their chance of treatment with one or more drugs being roughly 50%. This again shows the presence of patients with variable or discontinuous symptoms (Table 4.12).

Table 4.12 - *Distribution of patients by exposure level and type of treatment.*

NSAID treatment	Exposure level						Total	
	Low		Intermediate		High			
	No.	%	No.	%	No.	%	No.	%
MONOTHERAPY (1 drug)	64412	100	11658	45.1	8263	23.0	84333	66.8
POLYTHERAPY (>=2 drugs)	-	-	14175	54.9	27690	77.0	41865	33.2
Total	**64425**	**100**	**25833**	**100**	**35953**	**100**	**126198**	**100**

Hospital admissions for osteoarthritis.

Through the linkage of the prescription database with the hospital discharge database, patients exposed to NSAIDs who underwent a hospital admission for arthrosis or other arthropathies within the time period considered were identified. Overall, 323 patients underwent a hospital admission (0.3% of those treated with NSAIDs), and their diagnosis was arthrosis in 87% of these cases (280/323).

With respect to type and level of NSAID exposure, 66.3% of the subjects who underwent a hospital admission were chronic NSAID users, and 56% were high-exposure patients (Figure 4.9). Within a population of NSAID-treated patients, the likelihood of being admitted to hospital was significantly higher among chronic *versus* occasional users (0.5% vs 0.1%, $p<0.0001$) and increased with increasing exposure levels (0.5% among those highly exposed *vs* 0.2% and 0.1%, respectively, among patients at intermediate and low exposure).

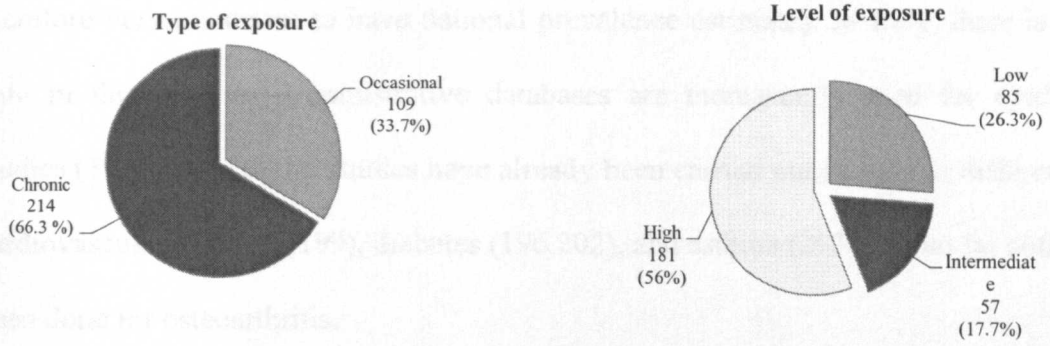

Figure 4.9: *Distribution of patients admitted to hospital by type and level of NSAID exposure.*

4.2.4 Discussion and conclusions.

In developed countries, osteoarthritis is one of the main causes of chronic disability. As a typical disease of the elderly, its prevalence is expected to rise owing to the ageing of the population (186, 200).

To date, no accurate prevalence estimates are available. The little information available in the literature derives from American studies, which indicates that osteoarthritis is suffered by 16 million people and that on average its prevalence within the adult population is 27.6% (diagnosed cases, to which 17.3% undiagnosed cases can be added) (201).

The elderly population is the most affected by the disease, with 80% of those over 75 years old showing symptoms of osteoarthritis. Autopsy results indicate that almost all those over 65 suffer some degree of cartilage damage (200). Osteoarthritis is a heterogeneous disease that has multiple causes. These are characterised by high clinical and epidemiological variability. Multiple risk factors are involved, and to plan adequate care programmes it is therefore very important to have national prevalence estimates. In Italy, there is a dearth of data in this respect. Administrative databases are increasingly used for epidemiological studies (192-199). Several studies have already been carried out in Italy in different areas, i.e. cardiovascular (195,197,199), diabetes (196,202), and asthma (203), but so far nothing has yet been done for osteoarthritis.

This study proposes a model investigation to identify the populations of patients from administrative databases (drug prescriptions and hospital discharge databases) to acquire information on specific problems.

The definition of 'disease-specific tracer drugs' is an essential qualification for this type of study. In the case of osteoarthritis, the tracer drugs were NSAIDs, which are very

often used to treat pain and inflammation; i.e. the symptoms that characterise osteoarthritis (185, 188-190).

By analysing the NSAID prescriptions according to a predefined protocol that also involved record linkage with hospital discharge forms, it was possible to identify a population of patients who can be considered (on the basis of their level and intensity of exposure) to be at 'high probability' of being affected by osteoarthritis. Specific attention was focused on chronicity, by developing a model of analysis that allowed the identification of chronically exposed patients. The population of 35,953 patients with a high probability of being affected by osteoarthritis indicated a 5.7% prevalence within the entire population covered by the LHA, and a 14.8% prevalence among subjects >65 years of age. The variability of the disease, and the presence in the sample of subgroups of patients with variable exposure both in terms of duration and intensity, indicate that the prevalence might well have been underestimated, since only patients with a high chance of the disease were included; i.e. those exposed to an intensive and prolonged treatment with NSAIDs. Beyond the (more or less conservative) precision of estimates, an important result of this study is the size of the sample identified (over 35,000 patients). Its relevance lies not only in the dearth of information in this area, but also in its potential representativeness of the problem and of the patients. Also, the sizes of the subgroups (e.g. high or low treatment intensity, use of monotherapy or polytherapy, age categories) outlining the different disease or risk groups were quite large, and in any case greater than those recruited for clinical trials. The analysis of the treatments prescribed, so far carried out in very general terms, show that in the majority of cases, a polytherapy approach is followed. This might indicate a variability in the therapeutic needs of the patients (according to the variability of the clinical picture), or a low treatment tolerance

and consequently the need for constant changes. Indeed, it should not be forgotten that most of the patients are elderly, and very likely to also be affected by other conditions as well as being treated with other drugs. The data presented here confirm previous knowledge (i.e., for instance, that the prevalence of this condition increases with age and particularly affects females). However, it also provides food for thought on some less well-known aspects, such as the frequency of access to the health care provider, and the need for hospitalisation notwithstanding treatment (indeed, hospital admissions are more common in the subgroup of high-intensity treatment). The development of the second phase of the study (the results of which will be illustrated in the following Chapter), was specifically aimed at the comorbidities and the occurrence of events such as hospitalisations for conditions that can be associated with NSAID use, and will allow further, more specific, insight.

Acknowledgments *This study was carried out within the Piedmont Region project: Evaluation of drug risk: the case of Coxib"*.

4.2.5 Appendix

Study protocol

The framework of the study

The pharmacological treatment of inflammation and pain of osteoarthritis is quite controversial:

- ✓ Because of its very variable intensity, duration, recurrence, and the possibility of symptom control;
- ✓ With respect to the efficacy of the therapeutic approaches;
- ✓ Because of the uncertainty of the estimates of its profile in terms of attributable costs of drugs and/or general care strategies (i.e., hospitalisations);
- ✓ Because of the variability of the behaviour of general practitioners (and of specialist consultants) facing clinically 'difficult' conditions, be it non-responders or subjects experiencing side effects.

The characteristics of the problem listed above suggested the undertaking of two separate albeit complementary sections of the project.

Hypotheses under study

- The data so far available on the efficacy-safety profile of Coxibs/ NSAIDs strongly suggest their substantial equivalence, which should lead to therapeutic decisions based on safety and cost criteria.
- However, prescriptions and general care in real life can differ substantially from expectations based on the available evidence.
- The two parts of the project were:

- Clinical care epidemiology: through an intensive and structured use of pharmaceutical databases, a description can be carried out of the prescription criteria of the index drugs, and of the extent of the exposure of the population;
- Observational prospective epidemiology, in which general practitioners are the actors-protagonists.

Operational programme

Transversal and longitudinal epidemiological profile of the exposure of specific populations to NSAIDs, both from a quantitative and qualitative perspective.

Objectives

a. Descriptive and comparative epidemiology of the annual prevalence of populations/ patients exposed to the different classes of NSAIDs and their main active principles.

b. Identification and epidemiological description of the populations exposed to other chronic treatments, assumed to be reliable indicators of comorbidity.

c. Construction of longitudinal cohorts of patients defined as above, according to the validated criteria.

Definition of index populations to establish annual prevalence

a. The population is stratified by age (>64 or ≤64), sex, and occasional vs chronic use of NSAIDs, as established by the number of boxes/year prescribed and by treatment duration.

b. Among chronic users, the elderly population is further subdivided into three age groups, i.e. 65-74, 75-84 and >85.

c. Within all these populations the distributions of other NSAIDs vs Coxibs are quantified.

Exposure of index populations to gastroprotective drugs.

The occasional or chronic exposure to NSAIDs is evaluated also with respect to the use of gastroprotective drugs, with particular attention to the timing of prescriptions, to identify pre-existing gastrointestinal problems and side effects.

Major comorbidity potentially influencing effectiveness and tolerability of NSAIDs

Exposure of index populations to other chronic treatments are assumed to be indicators of comorbidity (such as COPD, asthma, diabetes, cardiovascular diseases). These are also evaluated, insofar as they can affect the general clinical conditions of the patient as well as produce gastrointestinal side-effects (e.g. oral anticoagulants, long-term use of antibiotics, systemic steroids).

Longitudinal cohorts

The aim is to describe, over a period of 24-36 months:

- The history of exposure to the different drug groups relevant for osteoarthritis;
- The history of comorbidity in terms of chronic exposure to other treatments;
- The overall care history, including hospitalisations.

4.3 Epidemiology of complexity of patients with osteoarthritis.

4.3.1 Introduction.

Osteoarthritis (as discussed in Section 4.2) is a typical disease of the elderly population. Its prevalence increases with increasing age (201, 204-209). None of the diagnostic tests currently available for osteoarthritis is considered a '*gold standard*'. Most diagnosis of osteoarthritis is through X-ray, notwithstanding its low specificity (207,211). The lack of a direct correlation between joint symptoms and the degree of radiographic changes (211) complicates the diagnostic process, and therefore the therapeutic approach to the condition. The picture is further complicated by frequent comorbidities, which are also due to ageing (212), and which have a negative impact on the degree of disability of the patient (213, 214). The associated conditions with greater clinical impact are cardiovascular diseases, diabetes – with which osteoarthritis shares risk factors such as obesity and scarce physical activity – and depression, which can also affect quality of life and social relationships (215-218).

Moreover, the presence of associated conditions entailing different therapies complicates the treatment of osteoarthritis, owing to the potentially serious risks of drug interactions or toxicity increase. The burden of care of patients with osteoarthritis is therefore quite high, as well complex.

Symptom control, and particularly pain, is the main aim of drug treatment in osteoarthritis. For pain control, guidelines recommend to start with paracetamol, resorting to NSAIDs in more advanced or non-responding cases, and eventually to opioids (188, 219-222). Very advanced or serious cases can benefit from surgical arthroprostheses (223).

It is well known that in clinical practice NSAIDs are almost exclusively the drugs of choice, although in severe pain, weak opioids can be used (tramadol, or codeine associated with acetaminophen). In Italy, the reimbursement by the NHS of weak opioids for treatment of osteoarthritis pain started in 2005. These drugs can therefore be used as good tracers of osteoarthritis (219-223), and in the present analysis weak opioids with NSAIDs were used to better identify patients with chronic pain due to osteoarthritis.

The project presented here was based on this assumption, and the aim was to identify a cohort of patients with osteoarthritis in a sample of Italian LHA through prescription profiles, to describe their epidemiological and clinical characteristics, and through linkage with the hospital discharge database, to evaluate their complexity and the associated burden of care.

4.3.2 Methods.

The identification of the population suffering from osteoarthritis was carried out using and integrating the information from administrative databases (archive of prescriptions, hospital discharge databases, and NHS list) that are routinely available to Area Pharmaceutical Services of LHAs for the year 2005. The characteristics of these administrative databases and the record linkage technique have already been described elsewhere (Chapter 2).

The following criteria were used to identify patients with osteoarthritis:

- Age >54;
- Prescription of tracer drugs for osteoarthritis: NSAIDs (ATC code: M01A) and opioid analgesics (only tramadol and codeine, and the latter only in combination with acetominophen). Patients also exposed to specific rheumatoid arthritis drugs (methotrexate, leflunomide, infliximab) were excluded;

- Chronic exposure to the above-mentioned tracer drugs. Chronic exposure was defined as prescriptions for at least 3 boxes/year.

The patients identified were then examined according to class of treatment received, and therefore classified as exposed to NSAIDs only, opioid analgesics only, or combined treatment with NSAIDs and opioids. The analysis of the specific compounds used was carried out to identify patients who were always exposed to the same active principle ('stable or well controlled' patients in monotherapy), and those who received different active principles even if these belong to the same therapeutic group ('unstable or non-controlled' by polytherapy). Prescription intensity was also recorded, in terms of the number of prescriptions and of boxes received on average during the study year.

Comorbidity was assessed by taking into account the chronic prescription (3 or more boxes/year) of tracer drugs for specific conditions:

- Cardiovascular drugs (Gap: C);
- Anti-diabetics (A10);
- Respiratory agents (R03);
- Antidepressants (N06A);
- Anti-ulcer drugs (A02B);
- Antipsychotics (N05).

The severity-complexity of the patient condition and the relative burden of care entailed was evaluated according to intensity of treatments and specific comorbidities, frequency of access to general practitioners, and number of hospitalisations for all causes, as

well as for those correlated to osteoarthritis. To identify specific causes of hospitalisations, the ICD-9 codes 710-739 were used when recorded as primary or secondary diagnoses on the hospital discharge forms. All of the hospital admissions were examined with respect to the primary diagnosis and type of admission (regular hospitalisation, or day hospital). Finally, patients identified as suffering from osteoarthritis were compared with the general population >54 years of age of the LHA, albeit not presenting the criteria defined to establish osteoarthritis, so with respect to sex, age, comorbidity, visits/ consultations to general practitioners, and hospitalisations. The differences between the two populations were analysed using the *Population Effect Size Index* (ES), which allows the evaluation of a variable in very large samples (224). Cut-off values adopted for the ES index were 0.10 for categorical variables and 0.20 for continuous variables.

4.3.3 Results.

The sample included 138,813 subjects >54 years old, with 54.3% women. The patients identified as suffering from osteoarthritis according to our criteria numbered 16,808 (12.1%). As expected, as osteoarthritis is a typical condition that affects the elderly and particularly women, 78.7% of the patients were >65 years old and 65.8% were women (Table 4.13). On average, these patients received 5 prescriptions in a year (range: 1-68) and 5.5 boxes (range: 3-89) of tracer drugs for osteoarthritis. Overall, 15,529 patients (92%) received between 3 and 10 boxes, 1,116 subjects (7%) between 11 and 19, and 163 (1%) over 20 boxes. In the light of their high prescriptive intensity, the 1,279 patients receiving over 10 boxes are probably those whose symptoms were less effectively controlled and/or those who also had other problems; they were clearly older (52% over 75 years; 672/1,279), female (67%, 853/1279) and with

two or more comorbid conditions (54%, 696/1,279). The large majority of the patients (86.4%) were prescribed NSAIDs, with opioids alone prescribed to 12.3%, while 1.5% received combined NSAIDs/ opioid therapy. The use of opioids alone or in combinations with NSAIDs increased with age, at 10.8% among patients aged 55-64 years, 12% in the the 65-74-years group, 16% at 75-84 years, and 19.1% among people aged 85 years or over.

Table 4.13 – *Characteristics of the patients with osteoarthritis.*

Characteristics	No. (16808)	% (100.0)
Sex		
Male	5752	*34.2*
Female	11056	*65.8*
Age		
55-64	3587	*21.3*
65-74	6139	*36.5*
75-84	5462	*32.6*
≥85	1620	*9.6*
Prescriptive intensity		
Mean No. prescriptions (range)	5 (1-68)	
Mean No. boxes (range)	5.5 (3-89)	
Drugs		
NSAIDs	14523	*86.4*
Opioids	2039	*12.1*
NSAIDs+Opioids	246	*1.5*
Type of treatment		
Polytherapy	11538	*68.7*
Monotherapy	5270	*31.3*

The majority of the patients (68.7%) changed the active principle prescribed at least once, while only 31.3% received the same drug throughout the study period. The exposure to different drugs over the study year was slightly more common among women (70.3% vs 65.5% among men) and among younger patients (69.1% of the patients aged 55-64 years changed the drug at least once, compared to 62% among subjects aged 85 years or more).

Comorbidity.

The percentage of patients presenting comorbidities was relatively high, and as expected, this increased with age. Overall, only 20.3% of patients with osteoarthritis had no significant comorbidities, while 79.7% (13,397) had at least one accompanying condition, 26.2% (4,401) at least two, and 10.3% (1,724) three or more. Comorbidities were observed in 88% of the patients over 85 years, and in 66% of those aged 55-64 years. Age was also linked to an increase in the number of accompanying conditions: 13.7% of the subjects over 85 years had 3 or more associated conditions, while this proportion was only 5.7% among patients aged 55-64 years (Table 4.14). Among the comorbid conditions observed, the most frequent were cardiovascular diseases (69.8% of the patients) and gastrointestinal problems (22.4%), followed by diabetes (15.1%), respiratory problems (10%) and depression (9.2%). Antipsychotics were prescribed to 1.9% of the patients. The conditions more often associated with multiple comorbidities and that involved over 70% of the patients were cardiovascular and gastrointestinal conditions (27%), cardiovascular and diabetes (21%), cardiovascular and respiratory conditions (9.9%), and cardiovascular and depression (8.5%). Comorbidities had an influence on the management of pain, insofar as the patients with at least one comorbid condition were more often treated with opioids or opioids and NSAIDs, while these drugs

were prescribed to 8.5% (292/3,411) of subjects with no comorbidities; among people with comorbid conditions, their prevalence increased to 14.9% (1,993/13,397). Furthermore, patients with comorbidities more often experienced a change in their drug treatment. Exposure to different active principles over the study year involved 67% (2,290/3,411) of subjects without, and 72% (1,249/1,724) of those with, three or more comorbid conditions.

Table 4.14. – *Number of subjects with comorbid conditions by age.*

No. Comorbid conditions	Age								Total	
	55-64		65-74		75-84		>=85			
	No.	%	No.	%	No.	%	No.	%	No.	%
None	1220	*34.0*	1264	*20.6*	728	*13.3*	199	*12.3*	3411	*20.3*
1	1444	*40.3*	2760	*45.0*	2380	*43.6*	688	*42.5*	7272	*43.3*
2	718	*20.0*	1549	*25.2*	1623	*29.7*	511	*31.5*	4401	*26.2*
≥3	205	*5.7*	566	*9.2*	731	*13.4*	222	*13.7*	1724	*10.2*
Total	**3587**	***100.0***	**6139**	***100.0***	**5462**	***100.0***	**1620**	***100.0***	**16808**	***100.0***

Burden of care: GP access and hospitalisation.

The complexity of the population with osteoarthritis is also documented by the number of GP visits, i.e. in this case by the number of times the patients received a prescription from their GP. On average, each patient saw his/her GP 15 times over one year, with 25% averaging 9 visits, 50% 13 visits and75% 19 visits. The proportion of patients with ≥19 GP visits was higher among patients over 75 years (32.5%; 2,305/7,082), compared to younger subjects (22.2%; 2,161/9,726), and among therapeutically 'unstable' patients (29.1% of polytherapy

patients compared to 21.0% with monotherapy), and GP visits were markedly higher among patients with 3 or more comorbid conditions (70.7%), as illustrated in Table 4.15.

For hospitalisation, 31.4% of osteoarthritis patients required at least one hospital admission within the study year. Of the 5,237 patients hospitalised, 3,109 (59.0%) experienced only one hospitalisation; 1,777 (33.7%) experienced two or three, and 378 (7.3%) were admitted to hospital four or more times.

Table IV shows the number of hospitalisations by age, sex and presence of comorbid conditions. No major differences emerged in the rate of hospitalisations by age groups, while men appeared to be hospitalised more often than women (36% and 29%, respectively).

Table 4.15 – *Number of GP visits and patient characteristics.*

Characteristic	No. visits								Total	
	1-6		7-12		13-18		≥19			
	No.	%	No.	%	No.	%	No.	%	No.	%
Age										
55-64	800	*22.3*	1318	*36.7*	861	*24*	608	*17*	3587	*100.0*
65-74	807	*13.1*	1968	*32.1*	1811	*29.5*	1553	*25.3*	6139	*100.0*
75-84	460	*8.4*	1567	*28.7*	1658	*30.4*	1777	*32.5*	5462	*100.0*
85	139	*8.6*	468	*28.9*	485	*29.9*	528	*32.6*	1620	*100.0*
Sex										
Males	836	*14.5*	1643	*28.6*	1560	*27.1*	1713	*29.8*	5752	*100.0*
Females	1370	*12.4*	3678	*33.3*	3255	*29.4*	2753	*24.9*	11056	*100.0*

Characteristic	No. visits								Total	
	1-6		7-12		13-18		≥19			
Comorbid conditions										
None	1650	*48.4*	1318	*38.6*	346	*10.1*	97	*2.8*	3411	*100.0*
1	501	*6.9*	2981	*41*	2502	*34.4*	1288	*17.7*	7272	*100.0*
2	51	*1.2*	910	*20.7*	1579	*35.9*	1861	*42.3*	4401	*100.0*
≥3	4	*0.2*	112	*6.5*	388	*22.5*	1220	*70.7*	1724	*100.0*
Treatment										
Monotherapy	853	*16.2*	1856	*35.2*	1453	*26.6*	1108	*21.0*	5270	*100.0*
Polytherapy	1353	*11.7*	3465	*30.0*	3362	*29.1*	3358	*29.1*	11538	*100.0*
Total	**2206**	***12.1***	**5321**	***31.7***	**4815**	***28.6***	**4466**	***26.6***	**16808**	***100.0***

As expected, the presence of comorbidities increased the likelihood of hospital admissions. Among patients with 2 or more comorbid conditions, the proportion of patients with multiple hospital admissions was higher than that observed among patients with no comorbid conditions (35.5% *vs* 22%) (Table 4.16). Also, 3,169 subjects (60.1%) underwent regular hospitalisation, while 1,247 (23.6%) were included in a day hospital programme and 857 (16.3%) experienced both. Regular hospitalisation was more common among the very elderly than among subjects in the younger age group (76.4% and 54.9% respectively). The main cause for admission was diseases of the circulatory system (2,212 patients, 41.9% of those hospitalised), followed by diseases of the musculoskeletal system and connective tissue (1,309 patients, 24.8%), and then endocrine, nutritional and metabolic diseases and immunity disorders (1,119 patients, 21.2%). The causes of admission indicate that osteoarthritis-specific admissions (ICD-9:710-739) were more common among younger patients (Table 4.17).

Table 4.16 – *Number of hospitalisations and characteristics of patients.*

Characteristics	No. hospitalisations								Total	
	None		1		2-3		≥ 4			
	No.	%	No.	%	No.	%	No.	%	No.	%
Age										
55-64	2545	*71*	634	*17.7*	317	*8.8*	91	*2.5*	3587	*100.0*
65-74	4197	*68.4*	1144	*18.6*	652	*10.6*	146	*2.4*	6139	*100.0*
75-84	3652	*66.9*	1015	*18.6*	661	*12.1*	134	*2.4*	5462	*100.0*
≥85	1141	*70.4*	316	*19.5*	147	*9.1*	16	*1*	1620	*100.0*
Sex										
Males	3685	*64.1*	1142	*19.8*	731	*12.7*	194	*3.4*	5752	*100.0*
Females	7850	*71*	1967	*17.8*	1046	*9.5*	193	*1.7*	11056	*100.0*
Comorbidity										
None	2633	*77.2*	524	*15.4*	220	*6.4*	34	*1*	3411	*100.0*
1	5348	*73.5*	1220	*16.8*	597	*8.2*	107	*1.5*	7272	*100.0*
2	2720	*61.8*	952	*21.6*	589	*13.4*	140	*3.2*	4401	*100.0*
≥3	834	*48.4*	413	*24*	371	*21.5*	106	*6.1*	1724	*100.0*
Total	**11535**	***68.6***	**3109**	***18.5***	**1777**	***10.6***	**387**	***2.3***	**16808**	***100.0***

Table 4.17 – *Patients hospitalised for all causes and for osteoarthritis, by age.*

Age	Pts with osteoarthritis	All causes hospitalisation	OA cause (ICD9: 710-739) hospitalisation	% OA cause admissions/all OA pts	% OA cause adimssions/all pts hospitalised
55-64	3578	1042	342	9.5	32.8
65-74	6139	1942	517	8.4	26.6
75-84	5462	1810	390	7.1	21.5
≥ 85	1620	479	60	3.7	12.5

Moreover, 'unstable' patients with respect to drug treatment (polytherapy) showed a higher frequency of admissions due to osteoarthritis compared to 'stable' patients (monotherapy). The proportion of osteoarthritis hospitalisations for these patients was 9.2% (1,066/11,538) and 4.6% (243/5,270) respectively.

Comparison with the general population.

A comparison between patients with probable osteoarthritis and the general population >54 years old and without osteoarthritis was carried out with respect to the main variables defining the complexity: age, sex, comorbidity, and hospitalisations. The ES index confirmed the differences between these two populations, and significant differences were clearly seen for all of the variables considered (Table 4.18).

The picture tha emerges from this comparison is that the population suffering from osteoarthritis experienced a more complex-severe condition, both owing to older age and to a greater need for health care.

Table 4.18 – *Comparison of osteoarthritis patients with the general population.*

Variable	Osteoarthritis (%)	NON-Oseoarthritis (%)	Effect Size Index (ES)	p value
Mean age	72.3 (SD 10.09)	69.5 (SD 10.08)	0.29	
Women	65.8	52.8	0.23	<0.0001
Antidepressant drugs	9.2	5.1	0.16	<0.0001
Respiratory drugs	10.0	5.5	0.17	<0.0001
Cardiovascular drugs	69.8	47	0.41	<0.0001
Antidiabetics agents	15.6	9.2	0.17	<0.0001
Antiulcer drugs	22.4	9.9	0.35	<0.0001
Hospital admissions	31.4	19.6	0.26	<0.0001

4.3.4 Discussion and conclusions.

Through record linkage of different databases, the present study identified a population of subjects suffering from osteoarthritis. The size of the sample was much larger than that generally encountered in the literature. The analyses presented here document the complexity and the need for care of a population with osteoarthritis undergoing drug treatment, and allow the identification within that population of the subgroups with higher complexity and burden of care.

The prevalence of osteoarthritis within this population >54 years was 12.1%, which is lower than that reported by other studies (199,207-208). This is probably because all of those patients not needing drug treatment or for whom treatment with tracer drugs might only be occasional were excluded. As shown by other epidemiological studies (207,209,211), patients are mostly elderly (mean age, 72.3 years) and women (65.8%).

The complexity was well documented, since 79.7% suffered from at least one other comorbid condition, 97.2% saw their GP at least once a month, and 31.4% underwent at least one hospitalisation.

With respect to comorbidities, the comparison with the general population >54 years and without osteoarthritis indicates a high proportion of comorbid conditions, which were mainly cardiovascular conditions and diabetes. This was also confirmed by the literature, which indicated that osteoarthritis is one of the diseases with more associated conditions (213-216). The frequent use of anti-ulcer drugs may well be attributable to the prevention of the associated gastric toxicity (particularly among the elderly) with chronic use of NSAIDs, rather than to the presence of a comorbid condition. This may also explain the finding of a higher use of opioid derivatives, such as paracetamol-codein or tramadol, among older

subjects, i.e. those at higher risk of gastric toxicity as well as those with more comorbid conditions and therefore at higher risk of drug interactions. The choice of drugs used to control symptoms was complicated precisely by the high frailty of the population suffering from osteoarthritis. The development of models of study involving large sample sizes, so as to be representative of the complexity-severity as well as of the heterogeneity of the population, is therefore interesting. As well as what was already known, our study showed that within a population with osteoarthritis there are important differences, with variability of burden of care and care strategies in different subgroups of patients. Although older patients had more complex comorbidities and were frailer overall, younger patients with osteoarthritis require more hospitalisations due to the condition, as well as a more frequent need to change the anti-inflammatory drugs prescribed.

Results of prospective studies.

4.4 Epidemiology of anti-emetic treatments in oncology and factors associated to chemotherapy-induced nausea and vomiting: the results of the ETEO project.

4.4.1 Introduction.

Chemotherapy-induced nausea and vomiting (CINV) are among the most distressing side effects of cancer treatments, and they can have a negative influence on the quality of life of patients (225, 226). These symptoms may occur before chemotherapy (anticipatory CINV), within the first 24 hours after chemotherapy (acute CINV), and from 24 hours onwards (delayed CINV) (227).

Despite significant improvements in the field of anti-emetic therapy and in the recommended therapeutic guidelines, many patients still continue to suffer from CINV (228-231). Several factors affect the severity and pattern of CINV, such as the emetogenicity of chemotherapy agents, which is considered one of the most important factors (232), patient characteristics (with young and female patients under greater risk) and a previous experience of CINV (233,234).

The literature on CINV management is mostly focused on 'limited' populations that were selected on the basis of strict inclusion criteria, such as naïve patients (229,235-239), only one type of cancer (64), patients exposed only to the most emetogenic chemotherapeutic

agents (235-239), and only a specific phase of CINV or a specific setting of care (hospital, home) (228,235, 241-246).

The management of CINV is still problematic, in so far that it affects the quality of life of the patient, and in the most severe cases, the patient compliance with the antineoplastic treatment.

Given this framework, the ETEO (Epidemiology of anti-Emetic Treatment in Oncology) project was set up as a prospective survey of oncological patients undergoing chemotherapy in a routine care setting (day-hospital and home), in order to:

- investigate the incidence of CINV in each phase (anticipatory, acute and delayed) in a representative sample;
- identify prognostic factors for acute and delayed CINV;
- establish a multicentre and multidisciplinary surveillance of CINV management, involving all health professionals taking care of cancer patients (clinicians, nurses and hospital pharmacists).

4.4.2 Patients and methods.

The study was designed as a multicentre prospective observational survey, and it was performed in 23 Italian hospitals, where multidisciplinary working groups (clinicians, nurses and pharmacists) were established. All of the patients attending day hospital wards on six index days to receive a chemotherapy cycle were involved in the study.

In day hospital, a pharmacist or a nurse filled in a form, recording personal (gender and age) and clinical (cancer type, stage, ECOG performance status) characteristics, as well as treatments administered in day hospital and prescribed at home (antineoplastic and antiemetic drugs).

Antineoplastic agents were classified according to their emetogenic potential, as four categories: high (HEC), moderate (MEC), low (LEC) and minimal emetogenic chemotherapy (232,247). For chemotherapy combinations, the drug with the highest emetogenic risk was considered (239,248). Patients receiving only low and/or minimal emetogenic chemotherapy were considered as the same group (LEC).

The patients were interviewed:

- at the time of admission, about their experiences of anticipatory CINV (recording also antiemetic drugs assumed at home), and about CINV onset following the previous chemotherapy administration;
- at discharge, about the occurrence and severity of CINV during the hospital stay.

At discharge, in addition, a daily diary was provided to all of the patients to record episodes of nausea and vomiting. If patients were no able to fill in the diary, a pharmacist interviewed them by telephone. The patients defined the intensity of the symptoms on a numerical scale, from 0 (no nausea/ vomiting) to 5 (the worst nausea/ vomiting): scores of 1 or 2 were coded as mild, 3-5 as moderate-severe.

The frequency of anticipatory CINV (from 2 days before chemotherapy) was evaluated among patients non-naïve to chemotherapy. As reported in the literature (247,248),

acute CINV was defined as symptoms that occurred between chemotherapy administration up to 24 h later. Diaries with missing times of discharge were therefore excluded from the analysis, as no accurate distinction between acute and delayed CINV was possible.

Antiemetic therapy was evaluated according to the main guidelines available at the time of the survey (249,250). Specifically, to control acute CINV, the antiemetic therapy guidelines recommended:

- monotherapy or no treatment for patients exposed to LEC;
- 5HT3-antagonist with a corticosteroid for those with MEC or HEC.

To control delayed CINV, the guidelines recommended:

- no treatment for patients exposed to LEC;
- monotherapy or combination of a corticosteroid with a propulsive or a 5HT3-antagonist for patients with MEC;
- corticosteroid with a propulsive or 5HT3 antagonist for patients treated with HEC.

When the ETEO study was carried out, the new anti-emetics (aprepitant and palonosetron) were not yet registered in Italy, and so this is the reason why these drugs were not included.

The ETEO protocol was approved by the Ethics Committee of each participating hospital. Written and signed informed consent was obtained from all patients.

Statistical analysis.

For the whole sample, the patient baseline characteristics were reported as frequencies (percentage) and means ±standard deviation for categorical and continuous variables, respectively. The presence of anticipatory CINV was compared with Pearson's $\chi 2$ for categorical variables. To identify independent characteristics associated with acute and delayed CINV, Poisson regression models accounting for overdispersion were used. Covariates with an univariate p-value below 0.20 were entered into the final model. Results are expressed as incidence rate ratios (IRRs) and 95% confidence intervals (CIs).

Analyses were performed using SAS Statistical Package Release 9.2 (SAS Institute, Cary, NC). P-values < 0.05 were considered statistically significant.

4.4.3 Results.

A total of 662 patients were included by 23 Italian hospitals, with a mean number of 29 patients per hospital (range 12-40 patients) (exclusions are shown in Figure 4.10). Diaries were provided to all of the patients, and 591 (89.3%) were returned. The clinical and epidemiological characteristics of patients with and without the diary were similar, although patients who returned the diary had a better performance status (ECOG PS = 0: 66.7% vs. 45.1%, p <0.0001). Nineteen diaries were excluded from this analysis because of missing data.

The 572 patients analysed were predominantly female (55.9%), with a median age of 59.8 years. A large majority had a solid cancer (94.6%); 31.8% at an advanced stage (stage IV). Also, 31.8% had an impaired performance status (ECOG PS>=1). Patients naïve to chemotherapy represented 9.8% of the study sample (56/572), while 57% had completed at

least the second cycle. 28.7% of patients had already suffered from previous CINV (Table 4.19).

Table 4.19 – *Epidemiological and clinical characteristics of the study sample.*

Variables	No.	%
Gender		
Males	252	44.1
Females	320	55.9
Age		
<50	108	18.9
50-64	240	42.0
>=65	224	39.2
Mean age (SD)	59.8 (12.2)	
Cancer site		
Genitourinary	73	12.8
Respiratory/Thoracic	55	9.6
Haematologic/Blood	31	5.4
Digestive/Gastrointestinal	225	39.3
Breast	161	28.2
Other	27	4.7
Stage		
I-III	353	61.7
IV	182	31.8
Unknown	37	6.5
ECOG Performance Status		
0	388	67.8
>=1	182	31.8
Unknown	2	0.4
Chemotherapy cycle		
Naive	56	9.8
1st-2nd	178	31.1
3rd-6th	258	45.1

Variables	No.	%
>=7th	68	11.9
Unknown	12	2.1
Previous CINV		
No	393	68.7
Mild	62	10.8
Moderate-Severe	102	17.8
Unknown	15	2.6
Emetogenicity of chemotherapy		
Low (LEC)	223	39.0
Moderate (MEC)	292	51.1
High (HEC)	57	10.0
Total	**572**	**100.0**

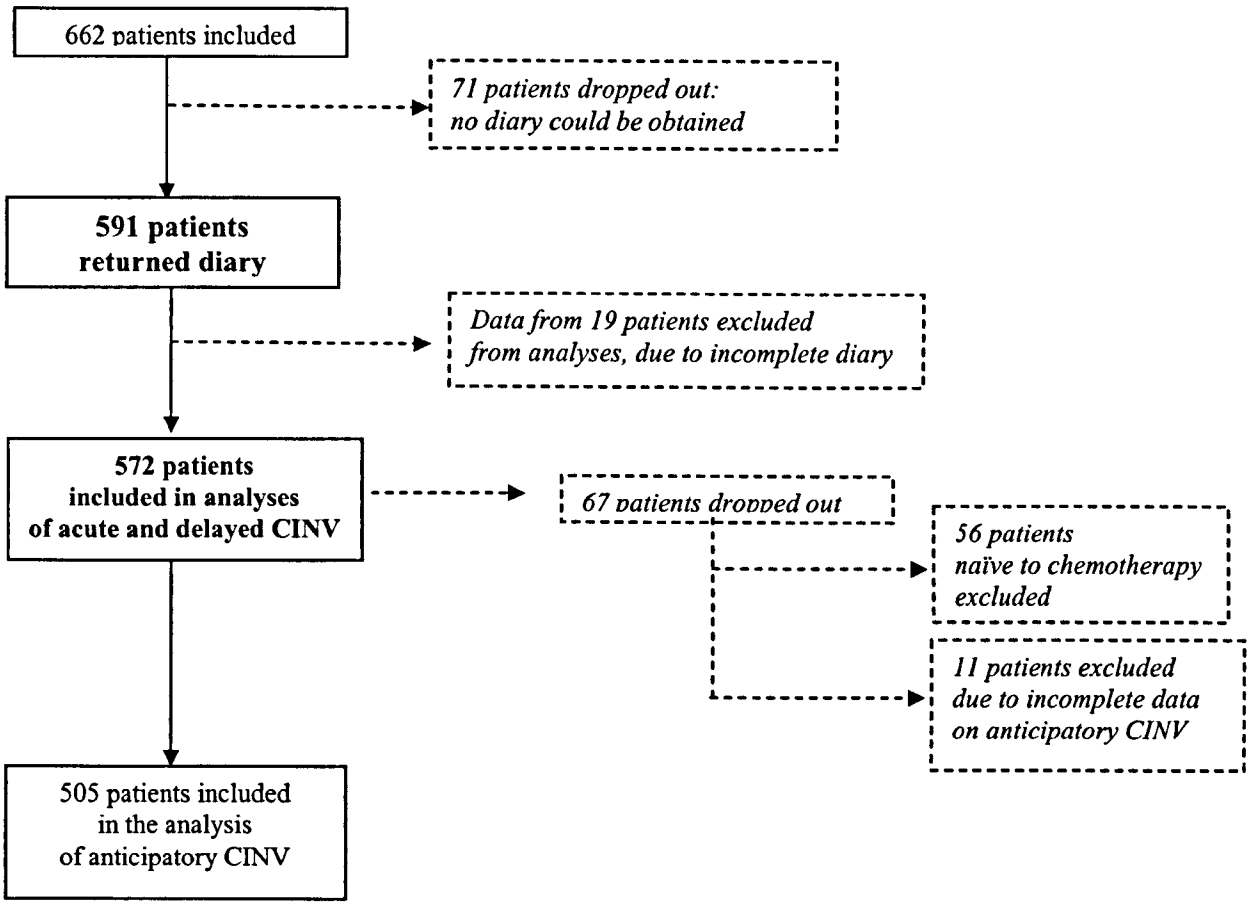

Figure 4.10: *Patient distribution chart.*

Anticipatory CINV.

Sixty-seven patients (13.3% of 505 non-naïve to chemotherapy) had anticipatory CINV (A-CINV). The comparison of patients with and without A-CINV (Table 4.20) showed that symptomatic patients were more frequently aged 50-64 years (58.2% vs 40.6%, respectively), at the 3rd-6th chemotherapy cycle (67.2% vs 48%) and with a previous experience of CINV (73.1% vs 26.3%; p <0.0001). In particular, patients with A-CINV had more commonly suffered moderate or severe CINV during the previous cycle than those without A-CINV (56.7% vs 14.8%; p <0.0001).

Table 4.20 - *Epidemiological and clinical characteristics of patients with and without anticipatory CINV (A-CINV).*

Variables	Pts with A-CINV	Pts without A-CINV	p value
	No. (%)	No. (%)	
Gender			*0.3799*
Males	26 (38.8)	195 (44.5)	
Females	41 (61.2)	243 (55.5)	
Age			*0.025*
<50	10 (14.9)	86 (19.6)	
50-64	39 (58.2)	178 (40.6)	
>=65	18 (26.9)	174 (39.8)	
Cancer site			*0.9599*
Genitourinary	7 (10.4)	55 (12.6)	
Respiratory/Thoracic	8 (11.9)	40 (9.1)	
Haematologic/Blood	3 (4.5)	27 (6.2)	
Digestive/Gastrointestinal	28 (41.8)	175 (39.9)	
Breast	18 (26.9)	121 (27.6)	
Other	3 (4.5)	20 (4.6)	
Stage			*0.7965*

Variables	Pts with A-CINV	Pts without A-CINV	p value
	No. (%)	No. (%)	
I-III	41 (61.2)	270 (61.6)	
IV	20 (29.8)	142 (32.4)	
Unknown	6 (9.0)	26 (6.0)	
ECOG Performance Status			*0.8463*
0	45 (67.2)	298 (68.0)	
>=1	22 (32.8)	138 (31.5)	
Unknown	-	2 (0.5)	
Chemotherapy cycle			*0.0165*
1st-2nd	18 (26.9)	156 (35.6)	
3rd-6th	45 (67.1)	210 (48.0)	
>=7th	4 (6.0)	61 (13.9)	
Unknown	-	11 (2.5)	
Previous CINV			*<0.0001*
No	18 (26.8)	317 (72.4)	
Yes	49 (73.1)	115 (26.3)	
Unknown	-	6 (1.3)	
Total	**67 (100.0)**	**438 (100.0)**	

Data are reported as frequencies (%). p values represent Pearson's $\chi 2$ test.

Acute CINV

Two-hundred-and-forty-six patients (43% of the sample) had acute CINV. These patients (Table 4.21) were younger, more frequently at the 3^{rd}-6^{th} chemotherapy cycle (52% vs 39.9%), more often with MEC (66.7% vs 39.3%), and had suffered more frequently from CINV, both during the previous cycle and in the anticipatory phase (23.6% vs 2.8%), than patients without acute CINV. The majority of the patients (348, 60.8%) received anti-emetic treatment, according to guidelines. Recommendations were followed in 55.3% of the cases with acute CINV and in 65% of those without acute CINV. Moreover, symptomatic patients

were more frequently undertreated than non-symptomatic subjects (33.3% vs 18.7%; p=0.0003) (Table 4.21).

The results of the univariate and multivariate analyses are reported in Table 4.22. Crude incidence rate ratios (IRRs) decreased with the patient age and increased with the intensity of previous CINV, and was higher among patients non-naïve to chemotherapy, patients with A-CINV, and patients with MEC and HEC, and among undertreated patients. The multivariate models shows that young age (<50 years), previous CINV experience, occurrence of A-CINV, and administration of MEC remained strong predictors of acute CINV. In particular, patients with a moderate-severe previous CINV experience had a 2-fold increased risk of acute CINV.

Table 4.21 – *Epidemiological and clinical characteristics of patients with and without acute CINV and delayed CINV.*

	Acute CINV			Delayed CINV		
Variable	**Yes**	**No**	**p value**	**Yes**	**No**	**p value**
	No. (%)	**No. (%)**		**No. (%)**	**No. (%)**	
Gender			*0.0529*			*0.0098*
Males	97 (39.4)	155 (47.5)		85 (37.4)	167 (48.4)	
Females	149 (60.6)	171 (52.5)		142 (62.6)	178 (51.6)	
Age			*<0.0001*			*<0.0001*
<50	62 (25.2)	46 (14.1)		60 (26.4)	48 (13.9)	
50-64	112 (45.5)	128 (39.3)		107 (47.1)	133 (38.6)	
>=65	72 (29.3)	152 (46.6)		60 (26.4)	164 (47.5)	
Cancer site			*0.1659*			*0.0719*
Genitourinary	32 (13.0)	41 (12.6)		31 (13.7)	42 (12.2)	
Respiratory/Thoracic	15 (6.1)	40 (12.3)		12 (5.3)	43 (12.5)	
Haematologic/Blood	12 (4.9)	19 (5.8)		14 (6.2)	17 (4.9)	

	Acute CINV			Delayed CINV		
Variable	Yes	No	p value	Yes	No	p value
	No. (%)	No. (%)		No. (%)	No. (%)	
Digestive/Gastrointestinal	97 (39.4)	128 (39.3)		86 (37.9)	139 (40.3)	
Breast	76 (30.9)	85 (26.1)		72 (31.7)	89 (25.8)	
Other	14 (5.7)	13 (4.0)		12 (5.3)	15 (4.3)	
Stage			*0.0776*			*0.0071*
I-III	160 (65.0)	193 (59.2)		157 (69.2)	196 (56.8)	
IV	68 (27.6)	114 (35.0)		59 (26.0)	123 (35.7)	
Unknown	18 (7.3)	19 (5.8)		11 (4.8)	26 (7.5)	
ECOG Performance Status			*0.2097*			*0.0253*
0	173 (70.3)	215 (66.0)		166 (73.1)	222 (64.3)	
>=1	71 (28.9)	111 (34.0)		60 (26.4)	122 (35.4)	
Non assessed	2 (0.8)	-		1 (0.4)	1 (0.3)	
Cycle of chemotherapy			*0.0093*			*0.3479*
Naive	15 (6.1)	41 (12.6)		19 (8.4)	37 (10.7)	
1st-2nd	73 (29.7)	105 (32.2)		64 (28.2)	114 (33.0)	
3rd-6th	128 (52.0)	130 (39.9)		110 (48.5)	148 (42.9)	
>=7th	26 (10.6)	42 (12.9)		30 (13.2)	38 (11.0)	
Unknown	4 (1.6)	8 (2.4)		4 (1.8)	8 (2.3)	
Previous CINV			*<0.0001*			*<0.0001*
No	120 (48.8)	273 (83.7)		116 (51.1)	277 (80.3)	
Mild	37 (15.0)	25 (7.7)		37 (16.3)	25 (7.2)	
Moderate-Severe	83 (33.7)	19 (5.8)		69 (30.4)	33 (9.6)	
Unknown	6 (2.4)	9 (2.8)		5 (2.2)	10 (2.9)	
Emetogenicity of chemotherapy			*<0.0001*			*<0.0001*
Low (LEC)	58 (23.6)	165 (50.6)		52 (22.9)	171 (49.6)	
Moderate (MEC)	164 (66.7)	128 (39.3)		148 (65.2)	144 (41.7)	
High (HEC)	24 (9.8)	33 (10.1)		27 (11.9)	30 (8.7)	
Anticipatory CINV			*<0.0001*			*<0.0001*
No	182 (74.0)	312 (95.7)		178 (78.4)	316 (91.6)	
Yes	58 (23.6)	9 (2.8)		46 (20.3)	21 (6.1)	
Unknown	6 (2.4)	5 (1.5)		3 (1.3)	8 (2.3)	

Variable	Acute CINV			Delayed CINV		
	Yes	No	p value	Yes	No	p value
	No. (%)	No. (%)		No. (%)	No. (%)	
Acute CINV						*<0.0001*
No				49 (21.6)	277 (80.3)	
Yes				178 (78.4)	*68 (19.7)*	
Antiemetic therapy			*0.0003*			*0.6557*
According to guidelines	136 (55.3)	212 (65.0)		109 (48.0)	158 (45.8)	
Overtreatment	28 (11.4)	53 (16.3)		89 (39.2)	148 (42.9)	
Undertreatment	82 (33.3)	61 (18.7)		29 (12.8)	39 (11.3)	
Total	**246 (100.0)**	**326 (100.0)**		**227 (100.0)**	**345 (100.0)**	

Table 4.22 – *Univariate and multivariate incidence rate ratios for acute CINV.*

Covariates	Unadjusted IRRs			Adjusted IRRs		
	IRRs	IC 95%	p-value	IRRs	IC 95%	p-value
Gender						
Males	1			1		
Females	1.21	(1.00,1.47)	0.0537	1.1	(0.9,1.35)	0.3642
Age						
<50	**1.79**	**(1.38,2.31)**	**<.0001**	**0.139**	**(1.06,1.82)**	**0.0177**
50-64	**1.45**	**(1.16,1.82)**	**0.0011**	1.21	(0.95,1.52)	0.1185
>64	1			1		
ECOG PS						
0	1					
>=1	0.87	(0.71,1.08)	0.2108			
Stage						
I-III	1			1		
IV	0.82	(0.66,1.02)	0.0779	0.83	(0.66,1.04)	0.0999
Cancer site						
Haematologic/Blood	1					
Solid	0.89	(0.58,1.39)	0.62			
Previous experience of CINV						

Covariates	Unadjusted IRRs			Adjusted IRRs		
	IRRs	IC 95%	p-value	IRRs	IC 95%	p-value
No	1			1		
Mild	1.95	(1.48,2.58)	<.0001	1.61	(1.21,2.15)	0.0012
Moderate-Severe	2.66	(2.16,3.29)	<.0001	1.92	(1.51,2.45)	<.0001
Anticipatory CINV						
Yes	2.35	(1.88,2.94)	<.0001	1.59	(1.24,2.03)	0.0003
No	1			1		
Chemotherapy cycle						
Patients naive	1			1		
Patients non-naive	1.68	(1.13,2.49)	0.0098	1.17	(0.77,1.76)	0.4651
Emetogenicity of Chemotherapy						
Low (LEC)	1			1		
Moderate (MEC)	2.16	(1.72,2.71)	<.0001	1.68	(1.29,2.19)	0.0001
High (HEC)	1.62	(1.13,2.32)	0.0087	1.35	(0.91,2)	0.1363
Antiemetic therapy vs guidelines (GL)						
According to GL	1			1		
Overtreatment	0.88	(0.65,1.2)	0.4347	1.04	(0.75,1.45)	0.8014
Undertreatment	1.47	(1.19,1.81)	0.0003	1.11	(0.88,1.39)	0.3836

Delayed CINV.

Two-hundred-and-twenty-seven patients (39.7% of the whole sample) were symptomatic in the delayed phase. The comparison between symptomatic and non-symptomatic patients (Table 4.21) shows that the former were more frequently women (62.6% vs 51.6%), under 64 years old (73.5% vs 52.5%), at a lower stage (69.2% vs 56.8%), with a good performance status (73.1% vs 64.3%) and exposed to MEC (65.2% vs 41.7%). More often, symptomatic patients had a previous experience of CINV, and particularly moderate-severe previous

episodes (30.4% vs 9.6%), as well as anticipatory (20.3% vs 6.1%) and acute (78.4% vs 19.7%) CINV.

Overall, 267 patients (46.7%) had received a prescription of an anti-emetic at discharge, and according to guidelines, 237 (41.4%) were overtreated and 68 (11.9%) were undertreated. No differences were observed between symptomatic and non-symptomatic patients (Table 4.21). Patients with acute CINV had almost a 5-fold risk of developing delayed CINV (Table 4.23). Significant univariate associations were also apparent for age (2.08 at <50 years, 1.68 at 50-64 years) and gender (1.32 among females). Patients receiving MEC and HEC, those with A-CINV, and those with previous CINV (both mild and moderate-severe) had roughly a 2-fold increase in risk. The multivariate analysis confirmed acute CINV as the strongest predictor of delayed CINV (IRR=3.85, 95%CI 2.96-5.02, p <0.0001), followed by high and moderate emetogenicity of chemotherapy (IRR=1.60 and IRR=1.36 respectively).

Table 4.23 – *Univariate and multivariate incidence rate ratios for delayed CINV.*

Covariates	Unadjusted IRRs			Adjusted IRRs		
	IRRs	IC 95%	p-value	IRRs	IC 95%	p-value
Gender						
Males	1			1		
Females	1.32	(1.07,1.63)	0.0096	1.17	(0.95,1.45)	0.1407
Age						
<50	2.08	(1.57,2.75)	<.0001	1.25	(0.94,1.66)	0.1276
50-64	1.68	(1.32,2.15)	<.0001	1.22	(0.95,1.56)	0.1187
>64	1			1		
ECOG PS						
0	1			1		

Covariates	Unadjusted IRRs			Adjusted IRRs		
	IRRs	IC 95%	p-value	IRRs	IC 95%	p-value
>=1	0.77	(0.61,0.97)	0.0254	0.88	(0.7,1.11)	0.2796
Stage						
I-III	1			1		
IV	0.73	(0.58,0.93)	0.009	0.85	(0.67,1.07)	0.1713
Cancer site						
Haematologic/Blood	1					
Solid	1.15	(0.75,1.75)	0.5151			
Previous experience of CINV						
No	1			1		
Mild	2.02	(1.52,2.7)	<.0001	1.29	(0.97,1.73)	0.0789
Moderate-Severe	2.27	(1.8,2.87)	<.0001	1.21	(0.95,1.55)	0.1279
Anticipatory CINV						
Yes	1.91	(1.48,2.46)	<.0001	1.03	(0.79,1.34)	0.8195
No	1			1		
Chemotherapy cycle						
Patients naive	1					
Patients non-naive	1.18	(0.82,1.7)	0.3773			
Emetogenicity of Chemotherapy						
Low (LEC)	1			1		
Moderate (MEC)	2.19	(1.71,2.8)	<.0001	1.36	(1.06,1.75)	0.0172
High (HEC)	2.07	(1.44,2.97)	<.0001	1.6	(1.11,2.29)	0.0111
Acute CINV						
Yes	4.82	(3.77,6.17)	<.0001	3.85	(2.96,5.02)	<.0001
No	1			1		
Antiemetic therapy vs guidelines (GL)						
According to GL	1					
Overtreatment	0.92	(0.74,1.14)	0.4367			
Undertreatment	1.04	(0.76,1.43)	0.8092			

4.4.4 Discussion and conclusions.

The characteristics of this study (multicentre survey, over six index days, using simple data collection forms), and the establishment of a multidisciplinary working group, allowed the quantitative and qualitative evaluation of a fairly large group of patients at relative low cost and over a short period of time. Our sample reflected the 'real' oncological clinical practice more than most populations reported in the literature (228,229,235-240,249), insofar as it included:

- all oncological patients (any cancer site or stage, cycle of chemotherapy, and emetogenic potential);
- all CINV phases;
- different contexts of care (hospital and home), thus obtaining a more representative picture of CINV management.

In this survey, 662 oncological patients were included and almost all (about 90%) were monitored at home (Figure 4.10). It was therefore possible to analyse the entire period at risk (anticipatory, acute and delayed phases) and to jointly evaluate different situations and contexts of care.

The occurrence of A-CINV was low (13.3%), as reported in the literature (244-246). Nonetheless, our results show that A-CINV has an important role on subsequent CINV phases, as it had a direct impact on the acute phase and an indirect impact (through the association between acute and delayed CINV) on the delayed phase. Given the dearth of literature data on A-CINV, these results are quite interesting.

More literature data are available on the acute phase, and good treatment guidelines have been proposed, particularly after the introduction in the clinical setting of $5HT_3$ antagonists (251-253). Almost all of the patients in our sample received a prophylactic anti-emetic therapy. However, too many patients continued to suffer from acute CINV. The incidence was similar to that reported in the literature (229,235), although it was slightly higher, probably owing to the inclusion of unselected oncological patients, not just those naïve to chemotherapy.

Although non-adherence to guidelines in the acute phase resuled in poor control of CINV (33.3% of symptomatic patients were undertreated), many of the patients treated according to guidelines were also symptomatic (55.3%). This may well reinforce the role of other risk factors. Clearly, both chemotherapy and patient-related factors are involved, since poor control of symptoms during the previous chemotherapy cycle was an important determinant for the occurrence not only of anticipatory CINV, but also for acute CINV.

As several studies have already shown (228,229,235), delayed CINV continues to be an unmet need in clinical practice: the unsatisfactory adherence to guidelines (46.7%) and the treatment prescribed at home, appear to be independent of the occurrence of acute CINV.

By itself, adherence to guidelines is not a sufficient guarantee against CINV, both in the acute and delayed phases. Evidence available in the literature (234,253-256) that are now confirmed by our data have indicated that poor control of symptoms in the acute phase increases the incidence of CINV also in the delayed phase. It is therefore important when an anti-emetic treatment is prescribed, to take into account the history and characteristics of the patient.

This study emphasises the need to improve the control of CINV during its entire course, from hospital to home. Although most studies believe acute CINV to be by-and-large under control, our data show that in clinical practice it is still a serious problem for many patients. An ongoing important challenge is the management of anticipatory and delayed symptoms that occur when patients are not under the direct observation of health-care professionals.

The ETEO project can be seen as a 'good' example of an epidemiological survey conducted in daily practice, as a normal component of routine clinical care. Similar studies need to be carried out periodically, given the ongoing introduction of both new antineoplastic drugs and new antiemetics, the therapeutic role of which (in terms of effectiveness and tolerability) need to be evaluated.

4.4.5 Appendix.

***ETEO working group**

Scientific committee

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4.5 Epidemiology of management of osteoarthritis in general practice: the results of the OMG project.

4.5.1 Introduction.

The intense debate that developed soon after rofecoxib was withdrawn from the market in 2004, and the subsequent reactivation of interest/ research on the safety profiles of all NSAIDs (178,180,182, 257-259), have increased the difficulties of therapeutic management of all conditions like osteoarthritis, that requests chronic use of anti-inflammatory or analgesic drugs.

The managements of osteoarthritis symptoms is mainly left to the general practitioners, who have to find the best therapeutic strategies for each patient, balancing the benefits and harms of drugs (260-262). Drugs tolerability has to be strictly monitored in these patients, because they are frequently frail and elderly (>75 years old), with other concomitants diseases.

An observational prospective study was carried out in collaboration with a sample of General Practitioners with the main objectives to describe:

- the management of osteoarthritis in a sample of Italian General Practices;
- the perception of GPs of osteoarthritis severity;
- patient perception of osteoarthritis severity and interference with daily life, their autonomy in drug management, and their ability to report eventual drug-related

problems, with the main objective of setting up a population/ patients-centred PV programme.

4.5.2 Study design.

The project was designed as a multicentre observational study that was carried out (Figure 4.11) with General Practitioners of six LHAs, located in six Regions (Abruzzo, Basilicata, Calabria, Trentino Alto Adige, Veneto and Piemonte), which are representative of the entire Italian territory. The study consists of a *cross-sectional phase* to produce an epidemiological picture of patients with osteoarthritis. All patients with an active problem of osteoarthritis attending General Practitioners over a period of four months (period of inclusion) have been included.

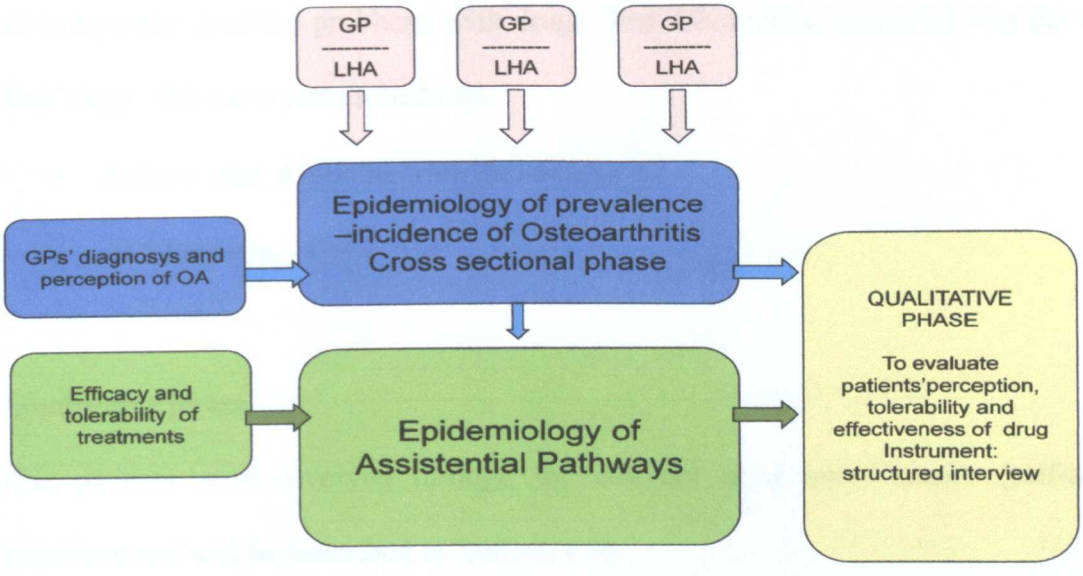

Figure 4.11: *Scheme of the study design.*

Prospective cohort.

A subgroup of patients selected from GPs among those with moderate-severe osteoarthritis was included in a cohort that was followed up for 12 months. The main objective of this phase was to produce an epidemiological picture of delivered care.

Patients were selected directly by GPs, as those who had moderate-severe osteoarthritis, according to their own interest in monitoring that particular patient for severity of osteoarthritis, the complexity of clinical general conditions, the difficulties in obtaining adequate pain control, etc. The reason of their inclusion in the prospective study had to be declared by GPs and reported in clinical recording files.

Follow-up visits.

Two follow-up visits were mandatory to evaluate the progression of osteoarthritis, the control of symptoms, eventual problems with drugs. The information requested was the same as the first visits. The visits were scheduled:

- At least after 4 months from inclusion;
- At 12 months.

Qualitative phase.

The patients were involved through the delivery of a questionnaire (self-administered interview and will be described in Section 4.7).

Data requested.

The GPs filled in the form, recording personal (gender and age) and clinical characteristics (new or old diagnosis, involved sites, signs and symptoms of osteoarthritis, prosthesis and functional limitation, comorbidities), and prescribed treatments (pharmacological and non-pharmacological). The most important sign and symptoms of OA were reported for each site involved. These were pain (transitory, continuous, nocturnal); oedema; stiffness: (morning stiffness, or after a short period of rest). Both pharmacological (drugs) and non-pharmacological strategies were suggested (e.g. diet, physical activity, rehabilitation) and were collected.

The GP evaluation of osteoarthritis severity was requested (low, moderate or severe) as well as pain intensities according to patients at the moment of visit. Patients defined the intensity of pain on a numeric scale, from 0 (no pain) to 4 (the worst pain).

Ethics Aspects.

The OMG (Osteoarthrosis Pathology in General Medicine) protocol was approved by the Ethics Committee of each participating LHA. Written and signed informed consent was obtained from all of the patients.

Statistical analysis.

Cross-sectional phase.

For the whole sample study, the patient baseline characteristics were reported as frequencies (percentages) and means ± standard deviations for categorical and continuous variables, respectively.

Moreover, the patient characteristics according to GPs' perception of osteoarthritis severity (mild, moderate, severe) and pain intensity reported by patients (mild, moderate, severe) were also recorded and compared with Pearson's $\chi 2$ for categorical variables.

To identify independent characteristics associated with GPs' perception of osteoarthritis severity and to account for the hierarchical nature of the data (patients within GPS) a multilevel multinomial logistic model was used.

Multilevel analysis is a methodology for the analysis of data with complex patterns of variability, with a focus on nested sources of variability (e.g. patients within general practitioners, longitudinal measurements of subject, studies measuring more than one outcome for each person). In these situations data are correlated: correct analysis requires that the correlations are accounted for. In the analysis of such data, it is usual to take account of the variabilities associated with each level of nesting: the variability between patients but also between general practitioners. Wrong conclusions can be drawn if either of these sources of variability is ignored. In particular, errors can result from analysing correlated data using standard linear or logistic regression. In general these techniques give estimates of regression coefficients that are similar to estimates generated by techniques that account for correlation. Although ignoring correlation usually introduces little bias into the estimates of regression coefficients, it can introduce substantial bias in the estimates of regression variances. Ignoring correlation when it exists can lead to incorrect inference about regression coefficients.

The multinomial logistic model is a straight forward extension of the logistic model for binary responses, which can accommodate multinomial responses (more than two categories). The multinomial model compares different levels of the dependent variable to a

base level. This makes the model considerably more complex, but also much more flexible. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

Longitudinal analysis.

To evaluate the longitudinal changes over 4 mounts and 1 year, respectively, in osteoarthritis symptoms, a longitudinal analysis was performed. To allow for the hierarchical nature of the data (repeated measurements within patients), and to control simultaneously for the possible confounding effects of the different variables, we used multivariate multilevel logistic models. In our longitudinal analysis, which evaluated changes of osteoarthritis symptoms, multilevel methods allowed the appropriate modelling for within-patient and between-patient variability. Among baseline patient characteristics, the following characteristics were considered: gender, age, and osteoarthritis severity. The results are expressed in terms of frequency (percentage) and the p value.

4.5.3 Results.

A total of 1,444 patients were included by 45 GPs, with a mean number of around 32 patients per GP. They were predominantly females (68.8%) and over 64 years old (63.4%) (Table 4.24); the great majority had at least one concomitant disease (81.4%), which were mainly cardiovascular (58.9%), depression (14.1%), diabetes (11.9%), COPD (9.5%), and osteoporosis (6.4%). Osteoarthritis was already known at the inclusion visit in 80.7% of cases, 8.5% already had a prosthesis, mainly knee or hip prosthesis. Functional limitations were reported in 27.3% of patients.

Among the old cases of osteoarthritis, GPs had already a confirmation of diagnosis in 96.7% of cases; these were mainly by X-ray and specialist diagnosis (48.4%) or only X-ray (33.1%).

For new diagnoses, the GPs requested confirmation in 79.6% of patients, which was instrumental confirmation (X-ray) in 89.3%, and both X-ray and specialist in 5.3%. Overall clinical signs and symptoms of osteoarthritis were considered sufficient for diagnosis in 2.3% of patients. According to symptoms, overall, 98.9% of patients had pain, 83% stiffness, and 43.7% oedema, which were both present in 18% of cases.

Table 4.24 - *Study sample characteristics.*

Characteritics	No (1444)	%
Age classes		
≤54	237	16.4
55-64	283	19.6
65-74	420	29.1
75-84	417	28.9
≥85	78	5.4
Missing	*9*	*0.6*
Gender		
Females	994	68.8
Males	450	31.2
Comorbidities		
None	268	18.6
1	565	39.1
≥ 2	611	42.3
Prostheses		
No	1231	85.2
Yes	128	8.9
Missing	*85*	*5.9*
Physical limitation		
No	1027	71.1
Yes	395	27.3
Missing	*22*	*1.5*
OA		
New diagnosis	279	19.3
Old OA	1165	80.7

Characteritics	No (1444)	%
Involved sites		
1	835	57.8
2	349	24.2
>=3	260	18.0
Pain		
Transitory	883	61.8
Continuous	654	45.8
Nocturnal	200	14.0
Edema	631	43.7
Stiffness		
Morning stiffness	854	71.2
After short period of rest	494	41.2

In 29.2% of patients, osteoarthritis was considered by GPs as mild, in 54.3% moderate, and in 16.5% severe. The comparison between the three different groups of osteoarthritis according to GPs' perception was documented in Table 4.25. Patients with severe osteoarthritis were more frequently:

- elderly (more than 50% of these patients were over 75 years old, vs 31.6% of moderate and 28% of mild),
- with two or more involved sites (36% three or more vs 16.8% and 10%, p <0.0001),
- with physical limitations (68.2% vs 25.1% of moderate and 8.3% of mild)
- with two or more comorbidities (54.4% vs 41.5% and 37.1%), than those with mild or moderate osteoarthritis with a statistically significant difference. p <0.0001.

Table 4.25 - *Patient characteristics by osteoarthritis severity.*

Characteristics	Mild (n=421)		Moderate (n=784)		Severe (n=239)		p value
	No	%	No	%	No	%	
Age classes							**<0.0001**
≤54	83	19.7	127	16.2	27	11.3	
55-64	85	20.2	178	22.7	20	8.4	
65-74	129	30.6	229	29.2	62	25.9	
75-84	100	23.8	214	27.3	103	43.1	
≥ 85	21	5.0	34	4.3	23	9.6	
Missing	*3*	*0.7*	*2*	*0.3*	*4*	*1.7*	
Gender							**0.0009**
Males	282	67	523	66.7	189	79.1	
Females	139	33	261	33.3	50	20.9	
Osteoarthritis							**<0.0001**
New diagnosis	91	21.6	169	21.6	19	8	
Already known	330	78.4	615	78.4	220	92.1	
Involved sites							**<0.0001**
1	279	78.4	449	57.3	107	44.8	
2	100	23.8	203	25.9	46	19.3	
≥3	42	10.0	132	16.8	86	36.0	
Symtpoms							
Pain	416	98.8	777	99.1	235	98.3	
Transitory	*335*	*80.5*	*476*	*61.3*	*72*	*30.6*	**<0.0001**
Continuous (not nocturnal)	*90*	*21.6*	*361*	*46.5*	*203*	*86.4*	**<0.0001**
Nocturnal	*56*	*13.5*	*95*	*12.2*	*49*	*20.9*	**0.0035**
Edema	76	18.1	426	54.3	129	54.0	**<0.0001**
Stiffness	284	67.5	686	87.5	229	95.8	**<0.0001**
Morning stiffness	*253*	*89.1*	*506*	*73.8*	*95*	*41.5*	**<0.0001**
After short period of rest	*67*	*23.6*	*250*	*36.4*	*177*	*77.3*	**<0.0001**

Characteristics	Mild (n=421)		Moderate (n=784)		Severe (n=239)		p value
	No	%	No	%	No	%	
No of symptoms							**<0.0001**
1	122	29.0	72	9.2	10	4.2	
2	243	57.7	319	40.7	104	43.5	
3	56	13.3	393	50.1	125	52.3	
Prostheses	14	3.3	58	7.4	56	23.4	**<0.0001**
Physical limitation	35	8.3	197	25.1	163	68.2	**<0.0001**
Comorbidities							**<0.0001**
None	92	21.9	140	17.9	36	15.1	
1	173	41.1	319	40.7	73	30.5	
>=2	156	37.1	325	41.5	130	54.4	

The results of polynomial logistic regression (Table 4.26) showed that the variables associated more often with severe or moderate osteoarthritis than with mild osteoarthritis were: the presence of prostheses, of continuous pain, of severe intensity (according to patients). The presence of these factors influenced GPs' perception of osteoarthritis severity, changing their judgment from mild to moderate or severe in a statistically significant way ($p < 0.0001$ in both comparisons). In particular, patient experience of severe pain was the most important factor that contributed to the GPs' evaluation of severity: patients reporting the worst pain had the highest probability of being considered as severe rather than mild, or being considered moderate rather than mild.

Table 4.26 - *Polynomial logistic regression results.*

Variables	Severe *vs* mild			Moderate *vs* mild		
	OR	95%CI	P-value	OR	95%CI	P-value
Age <65 vs >65	1.27	(0.67;2.43)	0.4711	0.91	(0.59;1.41)	0.6864
Gender: F vs M	1.21	(0.63;2.31)	0.5755	0.77	(0.50;1.19)	0.2431
Physical limitation: Si vs No	9.3	(4.33;19.97)	<0.0001	1.73	(0.94;3.18)	0.0805
Prostheses Yes vs No	**41.68**	**(14.18;122.49)**	**<0.0001**	**8.25**	**(3.16;21.55)**	**<0.0001**
Involved sites: ≥2 vs 1	1.72	(0.88;3.34)	0.1175	1.26	(0.77;2.05)	0.3497
Comorbidities						
1 vs 0	1.3	(0.54;3.13)	0.5697	1.06	(0.60;1.87)	0.8447
≥2 vs 0	1.27	(0.51;3.19)	0.6147	1.12	(0.61;2.05)	0.7257
Edema: Yes vs No	2.41	(1.19;4.88)	0.0139	1.63	(0.96;2.77)	0.0672
Pain						
Nocturnal vs transitory	3.53	(1.38;9.03)	0.0088	1.15	(0.61;2.15)	0.6482
Continuous (not nocturnal) vs transitory	**8.58**	**(3.92;18.80)**	**<.0001**	**3.03**	**(1.82;5.05)**	**<.0001**
Stiffness						
Morning vs no stiffness	5.47	(1.76;17.06)	0.0035	2.34	(1.30;4.21)	0.0044
After short vs no stiffness	11.36	(3.64;35.40)	<.0001	3.29	(1.69;6.40)	0.0005
Diagnostic confirmation: Yes vs No	1.95	(0.82;4.63)	0.1309	1.48	(0.89;2.46)	0.1449
Pain (by patients): Severe	**70.11**	**(18.13;271.08)**	**<.0001**	**47.94**	**(20.64;111.36)**	**<.0001**
Moderate	1.28	(0.36;4.59)	0.6986	9.58	(5.12;17.94)	<.0001

Therapeutic approaches.

The therapeutic management of osteoarthritis in the majority of patients (62.7%, n=1251) consisted of pharmacological and non-pharmacological prescriptions. Non- pharmacological approaches were different. Physical exercise was the most recommended approach (23.2% of cases), followed by rehabilitation (19.1%) and diet (12%).

Of 1,251 patients treated with drugs, 75.6% received only NSAIDs, 12.4% acetaminophen, and 7.3% opioids. Only 4.6% of treated patients took a combination of these drugs to control pain because of non-efficacy of monotherapy.

The distribution of therapies according to osteoarthritis characteristics indicated that among patients with mild osteoarthritis, GPs used NSAIDs (74.2%) or acetaminophen (21.5%) more frequently, even though 3% received opioids. Among severe patients, the rate of opioids prescription (18.5%) increased, as well as those of a combination of two different groups of drugs (10.8%).

The use of opioids was higher among elderly patients, as 12.2% of 75-84 years old vs 6% of those 55-64 years old, or patients with two or more comorbidities (9.9% vs 5.2% of those with one or 5.9% of those without comorbidities).

A great dispersion of prescribed drugs was documented by our study: the great majority prescribed diclofenac (17.4%), piroxicam (8.6%) or nimesulide (8%). Therapy was continued in 45.4% of patients (drugs already taken). A new therapy was prescribed in 41% of cases, chosen for its efficacy or tolerability (675 cases), only efficacy (209), or because of a specialist prescription (41 cases).

In 69 patients, a suspension of drug was necessary (6.2%) at the inclusion. Drug suspension was more frequent among patients with severe osteoarthritis, with more than two

comorbidities, over 75 years old. The reason for suspension was due to the non-efficacy of drugs, in the great majority (71.9% of cases). Nimesulide and acetaminophen were the drugs most suspended.

Prospective cohort.

GPs included 804 patients (55.7%) in the prospective phase, mainly to evaluate osteoarthritis progression (69%) or to monitor drug therapies (15.3%). They preferentially included patients with severe osteoarthritis ($p < 0.0001$), and those with 2 or more involved sites, with 3 or more symptoms. The follow-up at 12 months was completed for 472 patients (58.7% of patients included). After 12 months from inclusion, osteoarthritis was defined as stable in 68.8%, improved in 19.5% and worsened in 11.2% of patients.

Overall the evaluation of osteoarthritis severity in the follow-up period documented a progressive improvement of symptoms in our cohort from the first follow up visit. In particular, 4 months from inclusion, the percentage of patients with continuous pain decreased (38% vs 87.8% at baseline), as did that of patients with nocturnal pain (10.9% vs 22.1%); on the other side, the percentage of patients with transitory pain increased (30.2% vs 70.7%) indicating that pain still continued to be present, but in a less severe form. The same evolution was found for stiffness, as a portion consisted of patients who moved from stiffness after short periods of rest, to morning stiffness, documenting a positive trend.

Symptom frequencies and severity decreased at 12 months. The percentage of transitory pain increased, while that of nocturnal pain decreased, as well as a decrease seen for the percentage of stiffness after short periods of rest increased. The number of patients with morning stiffness increased, as well as a decreased seen for the percentage of patients

with moderate-severe pain at the moment of the visits. New pharmacological treatment was started in 53.5%, while 32.3% continued on the same drugs.

Among the cohort, 53 patients (11.2%) had to suspend drug treatment at least once. The suspensions were more frequent among severe (19.4% suspended a drug) than moderate (8.9%), among patients over 75 years (24.5% vs 11.8 of those 65-74 years), and among those with two or more comorbidities (13.5% vs 8.1% of those without).

Table 4.27 – *Symptoms evolution in prospective cohort.*

Variables	Baseline		Follow-up		Final Visit		P value
	N.	%	N.	%	N.	%	
Pain (presence)	172	97.7	92	89.3	91	88.4	**0.0105**
Transitory	*52*	*30.2*	*65*	*70.7*	*70*	*76.9*	***<0.0001***
Continuous	*151*	*87.8*	*35*	*38.0*	*35*	*38.5*	***<0.0001***
Nocturnal	*38*	*22.1*	*10*	*10.9*	*12*	*13.2*	
Edema	97	55.1	56	54.4	50	48.5	**0.0007**
Stiffness	168	95.5	86	83.5	79	76.7	**<0.0001**
Morning stiffness	*73*	*43.5*	*63*	*73.3*	*62*	*78.5*	*0.0002*
After short rest	*128*	*76.2*	*36*	*41.9*	*35*	*44.3*	*0.0363*
No of symptomns							
0- 1	8	5.1	17	16.5	29	28.2	
2-3	168	95	82	79.6	74	71.8	
Physical limitation	-	-	46	44.7	37	35.9	***<0.0001***
Patients' perception of pain							***<0.0001***
No pain -Mild	2	1.1	15	14.6	29	28.2	
Moderate -Severe	174	98.9	83	80.6	72	69.9	

4.5.4 Discussion and conclusions.

As also documented by my results here, osteoarthritis is a chronic disease that affects elderly patients and caused discomfort and disability (261). Almost all patients suffer from pain (more than 98% had pain), that is continuous in 45.8% and nocturnal in 14% of our sample.

The favorite diagnostic test to confirm osteoarthritis was X-ray (as also reported in the literature, 264,265), while there was a scarce need of specialist consultation (5.3% of new diagnoses). In selecting the drug therapies, our sample of practitioners changed drugs according to patient age and clinical condition. Opioids were more frequently used in 12.2% of 75-84 year olds vs 6% of those 55-64 years old, and in patients with two or more comorbidities (9.9% vs 5.2% of those with one, or 5.9% of those without comorbidities), because of their greater efficacy in controlling pain.

The GPs included consistent numbers of patients in the prospective cohort to control osteoarthritis progression and therapies. They preferentially included patients with severe osteoarthritis ($p < 0.0001$), those with 2 or more involved sites, and with 3 or more symptoms of osteoarthritis, documenting the need for strict monitoring of patients with a more complex clinical profile.

Main symptoms persisted in our sample even though their severity decreased. The severe cases were those who experienced more 'changes', that are due mainly to a lack of efficacy of the drug in controlling pain, followed by non-tolerability, documenting how difficult the management of symptoms among these patients is.

4.5.5 Appendix.

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4.6 Management of chemotherapy-induced nausea and vomiting at home: what do patients need?

4.6.1 Introduction.

Chemotherapy-induced nausea and vomiting (CINV) are the most common and discomforting adverse events in cancer patients (236, 266-268). The control of these symptoms is particularly difficult to achieve; many 'factors' can influence the occurrence and intensity of emesis: patient age, gender, and previous episodes of non-controlled acute emesis have been documented as determinants for the occurrence of delayed, as well as anticipatory, emesis (see section 4.2.1). Acute emesis can even cause the suspension or reduction of chemotherapy dose, where delayed treatment can worsen the patient quality of life and interfer with daily activities. This can also contribute to reducing patient compliance in subsequent cycles of chemotherapy. Moreover, its management at home causes further distress to many patients who are already in a critical situation (238, 269-271).

The objective assessment of vomiting would appear to be a relatively simple procedure and can be done by the patients. Assessment of nausea presents greater difficulties, as experience of nausea is a subjective phenomenon, so its assessment has relied almost entirely on patient reports.

A patient statement of satisfaction is considered a valid parameter in the evaluation of an anti-emetic regimen, because it reflects both beneficial (efficacy) and unwanted (toxicity)

effects of anti-emetic drugs. For these reasons, in the ETEO project, the patients were actively involved in the detection and description of episodes of delayed CINV at home, to assess the 'actual burden' of chemotherapy-induced adverse effects, and to obtain information on their own perception of the discomfort and the efficacy of the symptomatic drugs eventually taken.

4.6.2 Materials and Methods.

This was a 6-month epidemiological, observational, prospective study to evaluate the management of CINV in hospital and at home. At discharge, a daily diary was delivered to all of the patients to record episodes of CINV in the 3 days after chemotherapy administration. The pharmacists helped the patients who could not complete the diary, through a telephone interview 4 days after chemotherapy administration.

The patients had to report, for each day of follow up:

- the occurrence of each symptom, as nausea and vomiting;
- the intensity of the symptoms and the interference with daily life, using an analogue scale from 0 to 5 (0= no CINV, 5= worst intensity/ interference);
- the anti-emetics treatments eventually taken, and their efficacy.

The patients also had the possibility to report the occurrence of other symptoms or problems they suffered after chemotherapy.

4.6.3 Results.

A sample of 662 patients was surveyed in 23 hospitals. Daily diaries were delivered to all of these patients, and 591 were completed (89.3%), either directly (55%, n=325) or by telephone interviews (45%, n=266).

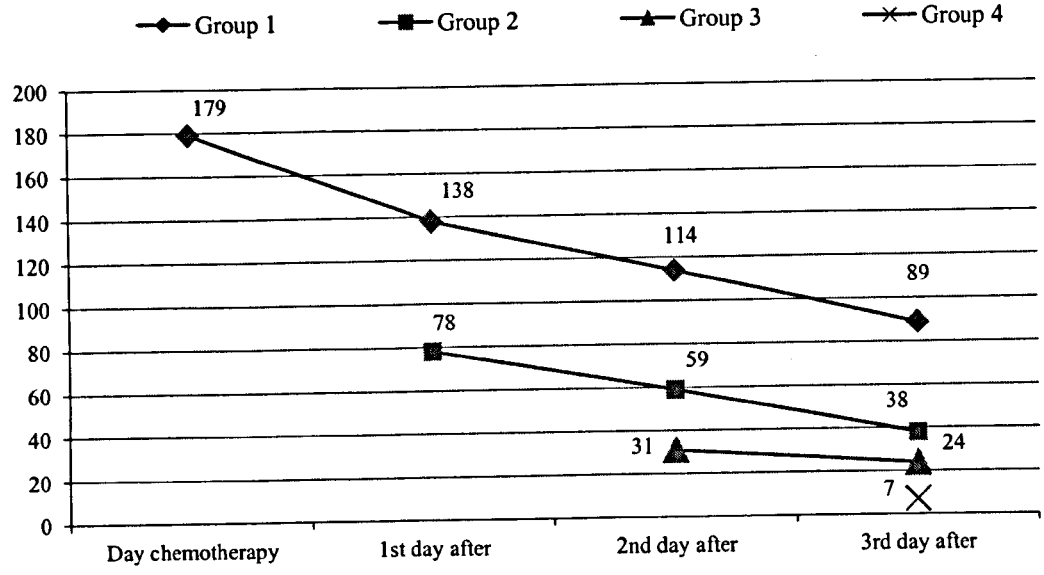
The patient distribution according to nausea and vomiting in the 3 days of follow-up is shown in Table 4.28: about 80% suffered nausea, while vomiting was reported by around 19% of our population, either alone or in combination with nausea. There was a decrease in the number of symptomatic patients over the 3 days: 36.5% on the first day, 35.2% on the second, and 27.9% on the third. In particular, the number of patients with vomiting reduced consistently from the first (49 patients) to the third (29 patients) day.

Analysis of subgroups of patients according to the day on which their symptoms began (Figure 4.12) showed that:

- 179 patients (30%) suffered from CINV the same day as the chemotherapy, and 89 were still suffering after 3 days, having an episode each day;
- 78 patients had CINV the day after chemotherapy, and 38 still had it after 3 days;
- 31 patients were symptomatic from the second day, and of these, 24 suffered the day after;
- 7 suffered CINV only on the third day.

Table 4.28 - *Distribution of symptomatic patients on each day of follow-up.*

Symptoms	1 day after chemotherapy		2 days after chemotherapy		3 days after chemotherapy	
	No.	%	No.	%	No.	%
Nausea	167	77.3	172	82.7	136	82.4
Nausea and vomiting	37	17.1	23	11.1	20	12.1
Vomiting	12	5.6	13	6.2	9	5.5
Total	**216**	**100.0**	**208**	**100.0**	**165**	**100.0**

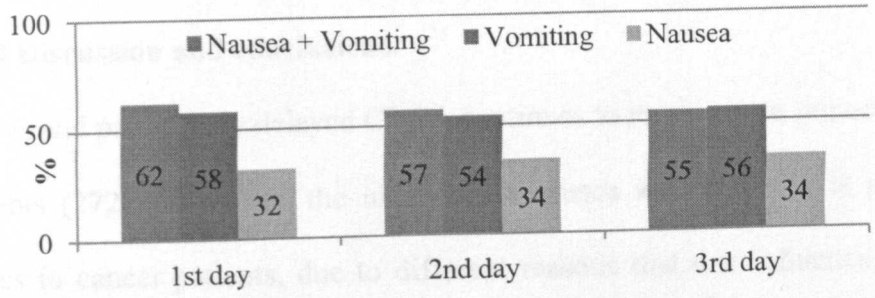


Note: Group 1: Group 1 = Symptoms from day of chemotherapy; Group 2 = Symptoms from 1st day after chemotherapy; Group 3 = Symptoms from 2nd day after chemotherapy; Group 4 = Symptoms on 3rd day after chemotherapy.

Figure 4.12: *Patient distribution by days of occurrence and length of symptoms.*

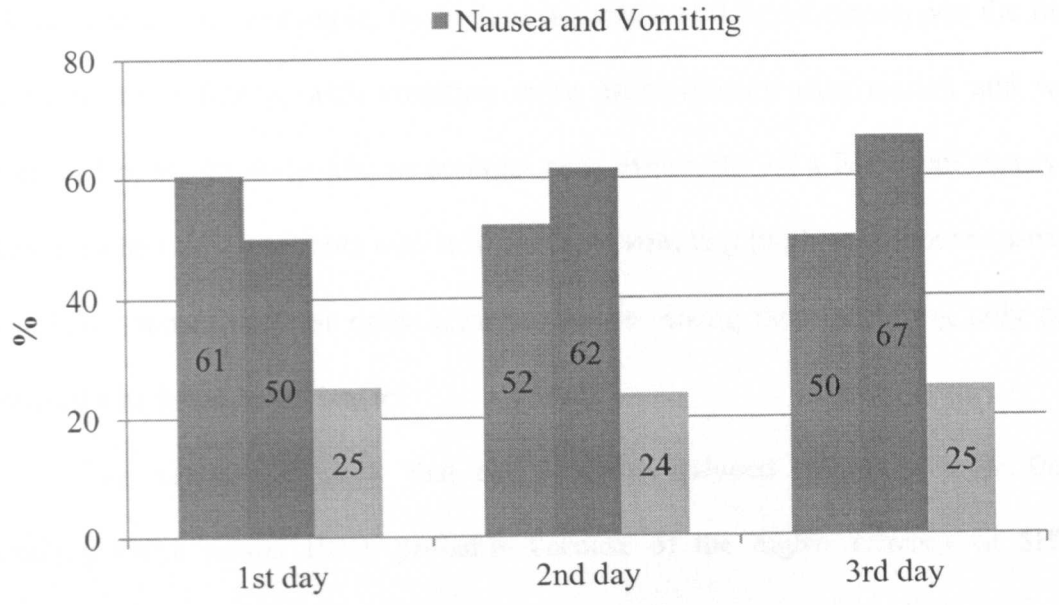
The intensity of the symptoms as reported by the patients showed that overall the proportion of patients who declared high-moderate intensity (regardless of symptoms) was the same over the 3 days: about 37% of those with CINV. Also, among the patients with vomiting (with or without nausea), those who had symptoms of high-moderate intensity were constant over the 3 days: around 54%.

There were differences on the basis of each of the reported symptoms: patients who suffered from vomiting (with or without nausea) indicated a higher grade of intensity on each days (Figure 4.13).The same results were obtained from the analysis of the interference with daily life (Figure 4.14). Vomiting was less frequent than nausea, but it was more discomforting and had a negative influence on daily life. Anti-emetic therapies were considered efficacious in controlling symptoms by 346 (58.5%): 40 in controlling only vomiting, 55 only nausea and 240 for both symptoms.



Note: *Percentages calculated on the total patients with nausea and vomiting, only vomiting, and only nausea on each follow-up day.*

Figure 4.13: *Percentages of patients with high-moderate symptoms on each follow up day.*



Note: *Percentages calculated on the total patients with nausea and vomiting, only vomiting, and only nausea on each follow-up day.*

Figure 4.14: *Percentages of patients with high-moderate interference with daily life.*

4.6.4 Discussion and conclusions.

CINV, and particularly delayed CINV, continues to represent an important problem for cancer patients (272). Moreover, the intensity of nausea and vomiting is particularly difficult to assess in cancer patients, due to different reasons that can influence it, such as the patient characteristics and the emetogenic potential of the chemotherapy agents (236, 269, 238). The results of various studies performed in the USA (267,236) and Europe (270-272) document an incidence rate of 25% to 38% for delayed vomiting and 55% to 60% for delayed nausea.

The present project aimed to establish the incidence of CINV in a sample of 591 patients treated in different Italian hospitals, and the results obtained confirmed the findings of previous studies: 43.8% of our patients had delayed emesis, and of these, 80% referred to

delayed nausea. In our sample, the highest incidence of delayed emesis was the first day after chemotherapy (36.5%), with vomiting more discomforting than nausea and with a more negative impact on daily life, in contrast with the results of a European survey (270,271). More than half of the patients who suffered from vomiting (with or without nausea) reported a significant impact on their daily activities, while among those suffering only nausea, 30% declared a high-moderate impact.

Our results also show that chemotherapy-induced nausea is more frequent than vomiting (80% *versus* 19%), probably because of the higher efficacy of $5HT_3$ receptor antagonists in controlling vomiting than nausea.

The study was carried out in routine clinical practice, monitoring a heterogeneous population. Despite this, it clearly documents that a consistent number of patients continues to experience CINV, and its prevention, as with the treatment, remains critical. Major attention to the incidence and duration of delayed nausea and vomiting will be necessary to achieve optimal control of this problem.

4.7 Patient perception of osteoarthritis and its therapies: the OMG questionnaire results.

4.7.1 Introduction and objectives.

One important aim of the OMG project was the active involvement of patients in the evaluation of osteoarthritis and of specific treatments.

Patient perception of pain, as well as of other discomforting symptoms of osteoarthritis, is part of the normal process of care, and their evaluation is taken into careful consideration by GPs, as demonstrated by results of epidemiological studies (section 4.2).

Patient participation in our study was realised with two main important objectives:

- To evaluate their experience of the illness, for the patient evaluation of health status and severity of osteoarthritis;
- To describe their autonomy in drug management, and the evaluation of eventual problems of tolerability of drugs.

4.7.2 Methods.

Pain intensity assessment.

Patients were involved in their pain intensity evaluation, as measured during GP consultation using a Likert scale.

Patient perception of osteoarthritis and its therapies.

A questionnaire was delivered by the GPs to their first 10 consecutive patients included in the cross-sectional study. All of the patients also received a pre-stamped, pre-addressed envelope to directly send back the compiled questionnaire.

The questionnaire was composed by five sections, each one with specific objectives. In the first group of questions, the patient perception/ knowledge of their own health status was explored, followed by a second group of questions on their perception of the severity of their osteoarthritis, and the interference with their daily activities and with their mood. The third and fourth sections were devoted to exploring their autonomy in the management of their drugs, and for any eventual drug-related problems (e.g. side effects, adverse events). The last group of questions were designed to explore the patient-doctor relationships, and any eventual unmet or unexpressed needs. The questionnaire answers were based on fixed choices, and for some questions the patients used a scale from scarce to good/ very good.

4.7.3 Results.

Perception of pain intensity.

All GPs asked the patients to describe the intensity of their pain at the moment of the consultation. Only 12 patients referred to no pain at baseline. Mild or moderate pain was referred to by 62.3% of patients, severe in 37.7%. The patients who declared severe pain were more frequently elderly, female, with two or more comorbidities, with already known osteoarthritis, poly-arthritis, and/or physical limitations than those with mild/ moderate pain.

The patients also suffered from pain during night rest and were considered as severe by GPs more frequently than by the patients with mild/ moderate pain.

Table 4.29 - *Pain severity according to patient characteristics.*

Characteristic	Mild (181)		Moderate (792)		Severe (454)		P value
	No. pts	%	No. pts	%	No. pts	%	
Age classes							**< 0.0001**
<54	26	14.4	143	18.6	66	14.5	
55-64	30	16.6	185	23.4	66	14.5	
65-74	64	35.4	228	28.8	124	27.3	
75-84	50	27.6	201	25.4	161	35.5	
> 85	9	5.0	32	4.0	33	7.3	
Missing	*2*	*1.1*	*3*	*0.4*	*4*	*0.8*	
Gender							**0.0052**
Females	119	66.8	527	66.5	340	74.9	
Males	62	34.3	265	33.5	114	25.1	
OA							**<0.0001**
New	28	15.5	192	24.2	57	12.6	
Old problem	153	84.5	600	75.8	397	87.4	
Involved sites							**<0.0001**
1	114	63.0	462	58.3	249	54.9	
2	49	27.1	216	27.3	78	17.2	
3 o più	18	9.9	114	14.4	127	28.0	
Pain	181	100.0	783	98.7	448	98.7	
Transitory	*162*	*89.5*	*548*	*70.0*	*159*	*35.5*	***< 0.0001***
Continuous	*24*	*13.3*	*272*	*34.7*	*356*	*79.5*	***< 0.0001***

Characteristic	Mild (181)		Moderate (792)		Severe (454)		P value
	No. pts	%	No. pts	%	No. pts	%	
Nocturnal	*12*	*6.6*	*95*	*12.1*	*93*	*20.8*	***< 0.0001***
Edema	29	16.0	387	48.9	211	46.5	**< 0.0001**
Stiffness	107	59.1	675	85.2	409	90.1	**< 0.0001**
Morning	*90*	*84.1*	*552*	*81.8*	*206*	*50.4*	***< 0.0001***
After short period of rest	*24*	*22.4*	*182*	*27.0*	*286*	*69.9*	***< 0.0001***
No symptoms							**< 0.0001**
1	69	38.1	90	11.4	36	7.9	
2	88	48.6	351	44.3	222	48.9	
3	24	13.3	351	44.3	196	43.2	
Prostheses	13	7.2	57	7.2	58	12.8	**0.0033**
Physical llimitation	3	1.7	147	18.6	243	53.5	**< 0.0001**
Comorbidities							**< 0.0001**
None	35	19.3	128	16.2	101	22.3	
1	71	39.2	359	45.3	130	28.6	
≥ 2	75	41.4	305	38.5	223	49.1	
Therapeutical approaches							
None	-	-	2	0.3	1	0.2	
Non pharmacological	77	42.5	65	8.2	11	2.4	
Pharmacological	40	22.1	182	23.0	144	31.7	
Both	64	35.4	543	68.6	298	65.6	

Questionnaire results.

The questionnaires delivered were 425, and 186 were returned (43.8%): 50 questionnaires were not completed, and for this reason they have been excluded in the analysis.

Of the 136 patients who completed the questionnaires, 69.8% were female, 50% were >70 years old; 50% were retired, and 42.6% were housewives. The majority (74.3%) declared to have at least one other disease, and 27.9% had two or more, which were mainly cardiovascular problems. In all, 52.2% of patients defined their health status as 'discrete', 19.9% 'satisfactory', while for 13.2% of patients this was 'poor'.

The combination of osteoarthritis symptoms as reported by the patients is illustrated in Table 4.30: 55.9% presented all of the symptoms of osteoarthritis: pain, stiffness and inability to autonomously carry out normal activities; while 25% suffered pain and stiffness.

Table 4.30 – *Symptom combinations.*

Symptom	No.	%
Pain, stiffness and inability	76	55.9
Pain and stiffness	34	25
Pain	13	9.6
Pain and inability	5	3.7
Stiffness	3	2.2
Inability	1	0.7
Stiffness and inability	1	0.7
Missing	*3*	*2.2*
Total	**136**	**100**

Overall, 94.1% suffered from pain and 83.8% from stiffness, and 61% had limitations due to osteoarthritis, for engaging in normal activities. Here, 40.6% of those with pain, 32.4% of those with stiffness, and 43.4% of those with inability referred to very high levels of these symptoms, thus documenting a situation of great discomfort.

The presence of these symptoms had influences on mood in 133 patients, and in 58.8% of cases this was recorded as considerably/ a lot; for 119 patients, their osteoarthritis interfered with sleep (51.5% considerably/ a lot). There were 93 patients who declared to not receive enough support from family members.

Almost all of the patients reported taking drugs (94.9%) to control their osteoarthritis. Among these, 64.3% took drugs only when they had severe pain, and 23.6% regularly. In 51.9%, they declared that he drugs were efficacious in controlling the pain, while 42.7% were not satisfied because they obtained poor or scarce pain control. Among our sample, 7.7% had already taken drugs not prescribed by doctors. Indeed, 20% of patients taking drugs autonomously changed their dose, without consulting any doctor, while 17.5% of the patients changed their dose after consulting a doctor. Here, 39% of patients declared that they had problems with drugs at least once, and the list of reported problems is given in Table 4.31.

Mainly of the patients had gastrointestinal problems, like nausea and vomiting, and 37.5% of patients with problems had made independent decisions without consulting their GP (e.g. interrupting the treatment, modifying the dose).

Table 4.31 - *Drug related problems reported by patients.*

Problems	No.	%*
Stomach pains	38	67.9
Nausea	17	30.4
Itching, rash, etc	13	23.2
Vomiting	4	7.1
Bleeding	2	3.6
Other	7	12.5
Total	**56**	**100**

*Many patients reported two or more problems

There were 67.6% of patients who were satisfied with the time available at each consultation to talk with their GPs; conversely, 8.8% declared that this time was scarce and were not satisfied.

4.7.4 Discussion and conclusions.

The results of the direct patient involvement in this project documented how discomforting osteoarthritis symptoms are for the affected population. These symptoms interfere with normal activities/ work, as well as with quality of life (interference with sleep or mood). Our data document that patients had a good perception of their own health status (in terms of comorbidities and related therapies):

According to therapies, our data document that more than 40% of patients were not satisfied with their prescribed therapies; 20% changed the dose of their prescribed drugs without consulting a doctor, and 7.5% declared that they took drugs without consulting a doctor, documenting their 'autonomy' in their therapy management. Also, in case of problems with drugs, there were some patients (around 31%) who felt that they had to 'do something' without consulting their GP. Indeed, 36% of our sample had used an alternative cure at least once, which was mainly manipulation or homeopathy, because of their unsatisfactory results with the traditional drugs.

The result obtained in this study document that the questionnaire that patients autonomously filled in is a good tool to directly involve patients in the description of their osteoarthritis symptoms and the interference with their life, and also to evaluate in a 'traditional' concept of PV all of the problems related to drug use.

CHAPTER 5

Final conclusions and perspectives.

5.1 To be effective, PV must be flexible.

The long history of the surveillance of drug safety documented very early on that its goals can hardly be reached and assured by concentrating its strategies and methods in one discipline, with the most-used name of 'pharmacovigilance'. Its highly focused, but at the same time limited, objective was further stressed: to monitor and control the non-toxicity, or safety, or tolerability aspects of individual drugs. The mainly regulatory settings where PV strategies were activated also implied a time frame that is based on the early post-marketing periods, although in principle, the voluntary reporting systems are *per se* extended, with no time limits to any moment in the life of the drug use.

One of the limits of traditional PV activities became more evident with the development of increasingly aggressive drug registration policies, where the variables included in the so-called 'conflict of interest' began to assumed a dominant (and little controllable) role, with the involvement of the full spectrum of actors: from industry, to investigators, to regulatory authorities, and to prescribers. his also began to even increasingly touch upon the associations with the patients, which had been hailed at their appearance as an independent resource for the protection specifically of the right of patients to safety (272-274, 276).

It then became further clear that a focus on safety cannot be separated from equal, and possibly more intensive, attention to the broader aspect of the rational use of drugs. Indeed, an excess of exposure of patients and populations to drugs prescribed beyond their targeted indications coincided with a qualitative and quantitative expansion of the denominators, with the inevitable consequence of an increased and uncontrollable possibility of affecting more sensitive, and/or more fragile, individuals or groups. The cases of Coxibs and antidepressants were 'perfect', model scenarios, out of the many that have been reported over the last 50 years (37,276).

Despite the many and successful experiences of independent initiatives, the key players in PV have remained those working along the regulatory chain. The main consequence of this has been a methodological rigidity. The strategies adopted for monitoring and assessing the ever wider spectrum of drugs, diseases and populations have remained substantially unchanged. The main preoccupation has been to minimise the costs and the time needed to produce a profile of the drugs that can be promoted as early as possible with no worries or warnings.

When a 'black box' has to be added at a very late stage of the life of a drug, sometimes with dramatic public health consequences, it is also clear beyond any reasonable doubt that the information given to the patients (who are by definition the centre of the problem) has been one of the most neglected aspects of PV.

5.2 Targeted patient- and population-based strategies of PV for an era of receptor-based targeted drugs.

One of the main objectives of the study presented here has been to provide a spectrum of real-life scenarios that were could be proposed and tested in a variety of contexts and with different research strategies and methods, with novel approach to and definition of PV.

The extensive critical review which opens this thesis is intended as a useful, propositive, 'inclusive' framework, wih the main advantage being to provide the conceptual and strategic justification for being very flexible in order to be well targeted on the specificity of the many heterogeneous issues. The field research projects planned and realised during these years through the linkage of administrative databases have documented that the periodical monitoring of these archives represents a powerful, relatively easily accessible, highly flexible tool to produce, at very low cost, the comprehensive history of well-defined populations where all major clinical events can be identified and qualified in terms of both effectiveness and severe adverse reactions.

As a first expression of the yield of targeted PV projects in the broader framework of epidemiology, the research programme was developed through prospective observational projects in two different contexts: the family practice setting of the OMG project (for osteoarthritis), and the complex context of oncological patients in a day hospital (the ETEO project). The reciprocal complementarity of the information that these contexts yielded was intended to become clearer when examined according the synoptical scheme of Table 5.1. Few comments are needed to highlight the take-home messages, which have been extensively discussed here in the previous chapters.

The OMG study was intended to describe the GP management of the chronic condition of osteoarthritis, by documenting the perception of osteoarthritis severity and the decision making processes, especially for drug therapy approaches.

Table 5.1 - *Synoptical scheme of the epidemiologic projects.*

Project	Context	Study population	Main objectives
OMG	General practice	Elderly patients with osteoarthritis	GP and patient perceptions of osteoarthritis severity. GP decision making processes, for both diagnostic and therapeutic strategies. Progression of osteoarthritis over a period of 12 months. Drug effectiveness in controlling symptoms and tolerability of osteoarthritis, according to GPs and patients.
ETEO	Oncological day hospitals ward	Cancer patients undergoing chemotherapy	Presence of specific chemotherapy side effects: nausea and vomiting. Effectiveness of anti-emetic therapies in controlling symptoms, and interference in daily activities.

One of the most original aspects of this project is perhaps represented by the active involvement of the patients for the comparison of their perception of their osteoarthritis severity with GP perception, and by the trace drug acceptability profile and the effectiveness in the control of symptoms. These were achieved through the testing and use of a very simple, readable, self-administered questionnaire that can became a routine tool in the monitoring and follow-up of patients with osteoarthritis in daily practice.

In this sense, the epidemiological surveillance of appropriateness and/or non-accessibility becomes an integral component of strategies that transform the evaluation of the impact of general recommendations or guidelines into a dialogue among the stakeholders, as a

dialogue that can be targeted to the problems and can be adequately tailored to the information needs of specific populations.

The re-collocation of drug vigilance in an epidemiological context where the accounts of what happens in the histories of individuals and populations prevail over the strict specialistic focus on 'side effects' can allow, and indeed requires, the participation of all of the actors, so not only of the health care circuits, but also of society. The ETEO project was realised with the collaboration of oncologists, nurses, and first and foremost, the patients. This clearly demonstrated that all of these actors can be involved in the production of knowledge on the 'subjectively perceived' and 'objectively documented' role of drugs in the management of such uncomfortable symptoms like nausea and vomiting.

5.3 The broader implications.

The therapeutic areas that were selected for investigation can be seen as specifically informative on this fundamental aspect of PV. They represent ambulatory and hospital settings where generally symptoms, problems and prescribing behaviour are more rarely monitored, as they are considered less relevant medically, and are left to empirically 'adjusted' decision processes. In this environment, specific information relating to the patients is, somehow, considered superfluous.

The language of a knowledge that is not swinging from peaks of alarm to even greater peaks of promotion becomes in this sense a shared communication of the uncertainties and limits of medicine, and includes close interactions with public opinion. Groups of patients, and their families, are able and motivated (as documented by the patient participation and the very large number of ETEO diaries filled in) to produce information on how treatments affect

the autonomy of their lives. They can hus provide greater reliability and more direct implications for timely adjustments of prescribing behaviours. Assessment of 'fragile' populations, as with oncological or elderly patients with different chronic diseases, should not come form the worries of the expert, but rather from the partners with whom the acual benefit-harm profile can be monitored. The qualitative and narrative accounts of patients must become less an object of *ad-hoc* studies, and more a routine component of an effort that is aimed at developing and shaping the language that give patients and citizens confidence about their right and duty to speak. This should remove the concept of only protests and claims, to allow them to be more of a part of the production of knowledge that can, and must, be incorporated in teaching and normative materials, and thus not only remain as an exercise that is rarely transferred into real life.

The most important result here is that instead of becoming a trap of specialised attention, drugs need to be given back their place in medicine, which is to be an indicator of the complex interplay between the 'formal' determinants of their prescriptions (such as official registered indications and evidence-based behaviours), the informal factors that are often even more important (such as patient expectations), and the conditions of the organisation of patient care.

5.4 Looking, and going, forwards.

For all of these reasons, my next research projects will continue in an oncological setting, in particular to monitor new oral antineoplastic agents. Many advantages have come from the introduction of these chemotherapies: obviously, they are more convenient to administer, they allows patients to avoid multiple office visits, and they give the patient a sense of control over

their own cancer care. Despite these advantages, it is imperative to note that there are multiple factors that can compromise patient safety and contribute to medication errors.

Moreover, additional risks associated with oral chemotherapies used in oncology arise from several factors, including the severity of the illness of many patients with cancer, the disproportionate representation of cancer among young children and the elderly, the toxicity and complexity of cancer treatments. For all of these reasons, the active involvement of patients/ caregivers in specific PV projects will provide a great contribution to the defining of the real compliance, and of the eventual non-adherence or drug-related problems. In particular, patients with cancer undergoing oral chemotherapies will be the protagonists of a specific PV project, to indeed evaluate adherence to prescribed regimens and eventual drug-related problems (e.g. adverse effects or reactions), and to define the overall patient satisfaction, or reasons of a lack of satisfaction, through the development and delivery of a specific patient diary.

The diary that allows the direct involvement of the patients can be further developed to analyse compliance, and to define eventual drug-related problems. This will involve a sub-group of patients who will actively contribute to the definition of the diary, in order to assure their understanding, from both the patient and the investigator points of view. The diary will be useful to monitor use of oral chemotherapies, and the eventual drug-related problems and reasons for non-adherence to prescribed regimens.

To become a routine component in the culture of care that can be shared by all of the actors concerned, PV will profit greatly from a mix of flexible and exchangeable methods and instruments that can be used in the various settings and for different objectives within epidemiology. This covers from the highly sophisticated and difficult to run, to the 'quick and

dirty', which can generate and test suspicious to be validated by capturing and analysing the information that is needed.

The emergence and widespread use of a language of PV that mimics more the narrative style of the daily life among 'peers' (where this term defines doctors, patients, nurses, and citizens beyond their professionals roles and competencies) should be considered as one of the most reliable and promising 'outcome measures' of a renewed season of PV.

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